Insights into digestion and absorption of major nutrients in humans

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Goodman BE. Insights into digestion and absorption of major nutrients in humans. Adv Physiol Educ 34: 44–53, 2010; doi:10.1152/advan.00094.2009.—Nutrient digestion and absorption is necessary for the survival of living organisms and has evolved into the complex and specific task of the gastrointestinal (GI) system. While most people simply assume that their GI tract will work properly to use nutrients, provide energy, and release wastes, few nonscientists know the details about how various nutrients are digested and how the breakdown products traverse the cells lining the small intestine to reach the bloodstream and to be used by the other cells of the body. There have been several recent discoveries of new transporters that likely contribute to the absorption of oligopeptides and fatty acids. In addition, details are being clarified about how transporters work and in what forms nutrients can be absorbed. The enzymes that digest basic carbohydrates, proteins, and fats have been identified in various segments of the GI tract, and details are becoming clearer about what types of bonds they hydrolyze. Usually, detailed information about the digestion of basic nutrients is presented and learned in biochemistry courses and detailed information about absorption via transepithelial transport of the breakdown products of digestion is studied in physiology courses. The goal of this Staying Current article is to combine the details of the biochemistry of digestion with the updated information about the physiology of nutrient absorption into one source for teachers of physiology. Insights are included about some of the diseases and conditions that can bring about malabsorption of food in the GI tract and their consequences.

carbohydrates; proteins; lipids; oligopeptide transporters; digestive enzymes; fatty acid transporters; teaching

TEACHERS OF UNDERGRADUATE PHYSIOLOGY COURSES may routinely assign students the following question: “Be able to describe in detail the steps in the entire mammalian gastrointestinal (GI) tract for digestion and absorption of ONE of the three nutrient groups.” In other words, tell how carbohydrates, proteins, OR fats are broken down (in which organs and by which enzymes) and then describe how the final breakdown products are absorbed (how they enter intestinal epithelial cells, cross the cell, and how they leave the cell, including whether they go into the bloodstream or the lymph system). The information presented in class generally has ~10 basic steps for the digestion and complete absorption of each major nutrient group. The diagrams found in most undergraduate physiology textbooks seek to clearly explain the details of these steps to the students.

Teachers in medical biochemistry for first-year medical students may give lectures on “Digestion and absorption of carbohydrates/proteins/fats.” Whereas undergraduate physiology textbooks tend to gloss over the details of the digestion of the various nutrients (what the enzymes are and how they work), medical biochemistry textbooks tend to gloss over the details of the transporters needed for the uptake of the breakdown products of the nutrients and the fate of the nutrients in the body. In addition, since the late 1970s, many of the details about digestion and transport have been elucidated. New transporters have been discovered (such as H+—oligopeptide transporters and fatty acid transporters). This review article seeks to highlight insights learned in studying the digestion, absorption, and transport of dietary carbohydrates, proteins, and lipids. The descriptions and diagrams are aimed at an audience of teachers of physiology who want to understand the details of the biochemistry of digestion and the physiology of epithelial transport of nutrient components. In addition, several clinical implications of defective processes are described to provide relevant examples to health career students.

Digestion and Absorption of Carbohydrates

The basic carbohydrates that are ingested by most Americans include simple sugars (glucose and fructose), disaccharides (lactose and sucrose), and complex carbohydrates (starch and glycogen). While carbohydrates are not essential in the diet, they generally make up ~40–45% of the total daily caloric intake of humans, with plant starches generally comprising 50–60% of the carbohydrate calories consumed (9). The major oligosaccharides consumed are the disaccharides sucrose and lactose, which comprise ~30–40% of dietary carbohydrates (4). Starch includes amylose and amylopectin and is a plant storage polysaccharide of >100 kDa. Starch is composed of the straight-chain glucose polymer amylose (with α-1,4 glycosidic linkages) and the branched glucose polymer amylopectin (with α-1,6 glycosidic bonds at a ratio of branched points to 1,4 glycosidic bonds of 1:20; see Fig. 1) (6). Glycogen is the polysaccharide storage molecule found in animal cells and is similar in structure to amylopectin except for a greater number of branch points in glycogen (6). Initial digestion of these complex carbohydrates begins with salivary α-amylase while still in the mouth. Both salivary and pancreatic α-amylases are endosaccharidases that are specific for internal α-1,4 glycosidic bonds (6). They have no effect on α-1,6 glycosidic bonds or on α-1,4 bonds of glucose molecules at the branch points or at the ends. The two α-amylases are secreted in active forms and are ~94% identical in amino acid sequences (4). Salivary α-amylase is deactivated by acid pH so that it remains active in the stomach only as long as it is protected from stomach acid. If trapped within a large bolus of food inside the stomach, salivary α-amylase can continue to digest complex carbohydrates until the bolus is broken up and exposed to stomach acid. Thus, up to 30–40% of the digestion of complex carbohydrates can take place before the food reaches the small intestine.

Inside the small intestine, pancreatic juice enters the lumen through the hepatopancreatic sphincter (sphincter of Oddi), and its high bicarbonate concentration begins to neutralize gastric acid. Concomitantly, pancreatic α-amylase reaches the lumen and actively continues to break down complex carbohydrates.
into maltose, maltotriose (isomaltose), trisaccharides, larger oligosaccharides, and α-limit dextrins (oligosaccharides with branch points) (9). Since di-, tri-, and oligosaccharides result from the hydrolysis of starch by α-amylase, additional digestion is required before the absorption of the monosaccharide breakdown products of starch can occur. These starch hydrolysis products must be further broken down by the disaccharidases found as membrane-spanning enzymes in the plasma membranes of the brush borders of intestinal epithelial cells (enterocytes) (4). Table 1 shows a summary of the major carbohydrates found in food with their typical sources, chemical bonds, brush-border membrane enzymes needed, and final monosaccharide products.

These brush-border membrane enzymes have varied specificities and varied locations within the small intestine. They are exoenzymes that cleave one monosaccharide at a time from the oligosaccharides or convert disaccharides into monosaccharides (6). One of the brush-border membrane enzymes is β-glucoamylase (also known as maltase), which hydrolyzes only α-1,4 glycosidic linkages between glucose molecules in maltose or beginning with the residue at the tail end of the polysaccharide (9). Another of the brush-border membrane enzymes

Table 1. Sources of carbohydrates, glycosidic bond types, membrane enzymes, and monosaccharide products

<table>
<thead>
<tr>
<th>Carbohydrate</th>
<th>Typical Sources</th>
<th>Bonds</th>
<th>Brush-Border Membrane Enzymes</th>
<th>Monosaccharide Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fructose</td>
<td>Fruit and honey</td>
<td>None</td>
<td>None</td>
<td>Fructose</td>
</tr>
<tr>
<td>Glucose</td>
<td>Fruit, honey, and grapes</td>
<td>None</td>
<td>None</td>
<td>Glucose</td>
</tr>
<tr>
<td>Amylopectin</td>
<td>Potatoes, rice, corn, and bread</td>
<td>α-1,4 and α-1,6</td>
<td>β-Glucosidase and isomaltase</td>
<td>Glucose</td>
</tr>
<tr>
<td>Amylose</td>
<td>Potatoes, rice, corn, and bread</td>
<td>α-1,4</td>
<td>β-Glucosidase</td>
<td>Glucose</td>
</tr>
<tr>
<td>Sucrose</td>
<td>Table sugar and desserts</td>
<td>α-1,2</td>
<td>Sucrase</td>
<td>Glucose and fructose</td>
</tr>
<tr>
<td>Trehalose</td>
<td>Young mushrooms</td>
<td>α-1,1</td>
<td>Trehalase</td>
<td>Glucose</td>
</tr>
<tr>
<td>Lactose</td>
<td>Milk and milk products</td>
<td>β-1,4</td>
<td>Lactase</td>
<td>Glucose and galactose</td>
</tr>
</tbody>
</table>

[Modified from Ref. 6.]
enzymes is the sucrase-isomaltase complex, which is actually two polypeptides (isomaltsase spanning the membrane with associated sucrase) (4). Isomaltsase (also known as limit dextrinase or debranching enzyme) hydrolyzes α-1,6 glycosidic bonds at the branch points in a number of limit dextrans and α-1,4 linkages in maltose and maltotriose (4). Sucrase hydrolyzes α-1,2 glycosidic linkages between glucose and fructose molecules and thus splits sucrose. Another of the brush-border membrane enzymes is the β-glycosidase complex, which includes lactase and glucosyl-ceramidase (9). Glucosyl-ceramidase splits β-glycosidic bonds between glucose or galactose and hydrophobic residues such as those found in the glycolipids glucosylceramide and galactosylceramide. Lactase splits β-1,4 bonds between glucose and galactose in milk sugar (9). Lactase deficiency (adult hypolactasia) is common in adults of many ethnic groups and leads to adult lactase levels that may be as low as 10% of those found in infants (9). Lactase-deficient small intestinal epithelial cells allow dietary lactose to reach the colon, where bacteria ferment lactose into gas and organic acids. This lactose produces an osmotic gradient, increasing water in the lumen. Thus, the gut walls are distended by the excess fluid, which increases peristalsis, causing further malabsorption and the frequent consequences of bloating and flatulence along with diarrhea (4).

Another brush-border membrane enzyme is trehalase, which hydrolyzes the glycosidic bond in trehalose, a small disaccharide uncommon in the American diet (9). Trehalase is found in insects, algae, young mushrooms, and other fungi and may cause gastrointestinal distress if consumed by an individual without adequate quantities of trehalase (1). Undigested trehalose arriving in the colon also causes an osmotic gradient leading toward loose stools and diarrhea followed by the digestion of trehalose by the microflora in the colon, producing gases (particularly hydrogen and methane, appearing in the exhaled air) (1). Trehalase is shorter than the other disaccharidases and has only one catalytic site to hydrolyze the α-1,1 linkage between glucose molecules in trehalose. It is still unclear how variable the duodenal trehalase activity may be in the human population; however, studies with Eskimos in Greenland and with people in Finland have identified both self-proclaimed mushroom-intolerant and trehalase-deficient individuals (1).

Pancreatic α-amylase acts mostly in the duodenum shortly after its entry through the hepatopancreatic sphincter and generates maltose, maltotriose, and α-limit dextrans from complex carbohydrates (6). Sucrase-isolamtsase and β-glycosidase have a high distribution and activity in the proximal jejunum, whereas glucoamylase has its highest activity in the proximal ileum (9). Thus, the spatial distribution of these disaccharidases (little activity in the duodenum and distal ileum and none in the large intestine) maximizes their activity to coordinate with the segments of the small intestine where glucose transporters predominate (4). These disaccharidases thus contribute to the phenomenon known as membrane digestion and provide monosaccharides for absorption across epithelial cells.

Once monosaccharides result from the digestion of carbohydrates by α-amylase and the brush-border membrane enzymes, the monosaccharides are taken up by the enterocytes via specific transport proteins that facilitate the transport of the d-isomers (but not L-isomers) of hexoses (4). d-Glucose and d-galactose are taken up by the Na⁺-coupled secondary active transport symporter known as Na⁺-glucose transporter 1 (SGLT1). SGLT1 is a high-affinity Na⁺-glucose transporter with 12 transmembrane-spanning α-helical domains and 662 amino acid residues with a mass of ~74 kDa (15). Its $K_m$ for sugar transport is a function of the Na⁺ concentration, and its stoichiometry is 2 Na⁺ for every d-glucose molecule (15). In the absence of Na⁺, d-glucose binds to SGLT1 with a much lower affinity ($K_m$ > 10 mM), but in the presence of Na⁺, a conformational change allows sugar to bind with high affinity ($K_m$ << 0.5 mM). When the intracellular Na⁺ concentration is low (~10 mM), Na⁺ dissociates from its binding site, causing the transporter affinity for d-glucose to decrease, and the sugar is released into the cytoplasm of the cell. The transporter must complete its cycle by undergoing a third, much slower transition to reorient the binding sites to the extracellular surface (15).

Thus, SGLT1 takes advantage of the Na⁺ gradient (i.e., low intracellular Na⁺ concentration) that is created by basolateral Na⁺, K⁺-ATPases to bring hexoses into the enterocytes. Since SGLT1 moves 2 Na⁺ with each d-glucose, it is capable of generating a glucose concentration gradient across the luminal membrane of 10,000-fold (3). Subsequently, d-glucose can leave the cell on the basolateral side of the cell via facilitated diffusion transporters [glucose transporters (GLUT2s)] from a high concentration inside the cell to a low concentration outside the cell (4). GLUTs are integral membrane transport proteins folded into 12 transmembrane-spanning α-helices that form a central aqueous channel for the movement of the substrate (d-glucose, d-galactose, or fructose) across the lipid bilayer. Of the five original GLUTs, only GLUT2 and GLUT5 are able to transport fructose, and GLUT5 has a very limited capacity for transporting d-glucose (12). GLUT2s are distinguished by being a low-affinity, high-turnover transport system with a $K_m$ in oocytes of 11 mM. GLUT2s are found in intestinal and kidney basolateral membranes (predominantly), in the liver, and in β-cells of the pancreas and mediate both the uptake and efflux of glucose, galactose, or fructose (12).

However, fructose is not transported by SGLT1 but rather is taken up on the brush-border side of the enterocyte by the specific facilitated diffusion transporter GLUT5. GLUT5s exhibit the weakest homology to other members of the GLUT family of all GLUTs and serve primarily as fructose transporters with a $K_m$ of 6 mM (12). They are found in the membranes of fructose-metabolizing tissues, including the brush-border membranes of intestinal cells and the membranes of sperm. They are likely the primary route for dietary fructose uptake in the small intestine. The intracellular conversion of fructose into glucose and lactic acid maintains its low intracellular concentration, aiding its continued absorption via facilitated diffusion from the lumen. As the bloodstream adjacent to the intestinal epithelial cells continuously removes the sugars that traverse entire enterocytes, glucose, galactose, and any remaining intact fructose easily exit the cells down their concentration gradients through facilitated diffusion GLUT5s without the use of cellular energy. Figure 2 shows a summary diagram of the steps involved in the digestion and absorption of carbohydrates.

Clinical example. Glucose-galactose malabsorption is a rare genetic disease in which the patient has defective intestinal d-glucose and d-galactose absorption (15). It presents as neonatal onset of severe, watery diarrhea, which can result in death.
unless water and electrolyte balance is quickly restored. Complete removal of glucose, galactose, and lactose from the diet stops the diarrhea within 1 h. Molecular studies have shown that multiple mutations in SGLT1 lead to glucose-galactose malabsorption in the small intestine; however, those patients with low glucose absorptive capabilities do not have glycosuria (glucose in the urine) because kidney proximal tubule epithelial cells (as opposed to enterocytes with only SGLT1 in healthy individuals) use both SGLT1 and SGLT2 for the uptake of glucose in the filtrate (4) and SGLT2 is not mutated simultaneously.

Fig. 2. Summary of the basic steps involved in carbohydrate digestion and absorption with important enzymes and transporters. The steps are explained in more detail in the text. SGLT1, Na⁺-glucose transporter 1; GLUT, glucose transporter. [Modified from Ref. 13.]

Digestion and Absorption of Proteins

The total daily protein load is ~70–100 g of dietary protein and 35–200 g of endogenous proteins, including the digestive enzymes and dead cells (6). A variety of proteolytic enzymes is necessary to break down dietary proteins into amino acids and small peptides since each enzyme has specificity for different types of peptide bonds. Endopeptidases attack certain internal bonds and result in large polypeptides, whereas exopeptidases cleave off one amino acid at a time from either the carboxy or amino terminus of the polypeptide or protein.
Consumed proteins or polypeptides begin to be broken down in the stomach under the action of the protease pepsin (4). Pepsin is secreted by chief cells in the gastric mucosa as pepsinogen, a larger inactive form of the enzyme, also known as a zymogen. Gastric acid (HCl, secreted by the parietal cells) alters the conformation of pepsinogen so that it can cleave itself and become active pepsin in the stomach. Gastric acid also denatures the proteins, which partially unfolds them so that proteases have better access to their peptide bonds. Pepsin (an endopeptidase) in the stomach begins to hydrolyze proteins at various cleavage points to smaller polypeptides (6). Pepsin has a higher specificity for cleaving peptide bonds in which the carboxyl group is provided by aromatic amino acids such as tyrosine, phenylalanine, tryptophan, and leucine (6). Although pepsin can partially digest 10–15% dietary protein in the stomach, pepsin hydrolysis is not necessary for survival (patients live with complete gastrectomy) (4).

As the chyme (partially digested food) enters the small intestine, pancreatic protease enzymes are excreted through the hepatopancreatic sphincter along with pancreatic bicarbonate. The bicarbonate begins to neutralize stomach acid and raises the pH to a more optimal level for the activity of pancreatic proteases. Pancreatic proteases are all secreted as zymogens so as not to become active while inside the pancreas and thus cause pancreatitis. The zymogen trypsinogen is cleaved to form trypsin by enteropeptidase (formerly known as enterokinase), a jejunal brush-border enzyme that may be released by the action of bile salts (9). Trypsin then catalyzes the cleavage of the other zymogens to their active forms. The pancreatic proteases (trypsin, chymotrypsin, elastase, and carboxypeptidases) cleave the polypeptides into oligopeptides and amino acids (Table 2). Trypsin, chymotrypsin, and elastase are serine proteases and act as endopeptidases (9). Trypsin is the most specific and cleaves peptide bonds next to lysine or arginine. Chymotrypsin is less specific and cleaves peptide bond adjacent to hydrophobic amino acids. Elastase cleaves elastin and peptide bonds adjacent to alanine, glycine, and serine.

The oligopeptides remaining after the action of these endopeptidases are attacked by exopeptidases, which cleave one amino acid at a time from one or the other end of the chain. The carboxypeptidases remove amino acids from the carboxyl ends of peptide chains (carboxy terminus) with carboxypeptidase A preferentially releasing valine, leucine, isoleucine, and alanine and with carboxypeptidase B releasing the basic amino acids arginine and lysine (6). The breakdown products of protease digestion of polypeptides and proteins are 30% free amino acids and 70% oligopeptides (2–8 amino acids) (4). Some of the oligopeptides are further hydrolyzed at the amino terminus by aminopeptidases located on the brush-border membranes to free amino acids and di- and tripeptides. Specific transport proteins facilitate the uptake of amino acids and di- and tripeptides across the brush-border membrane of the absorptive enterocytes.

The general properties of amino acid transporters are that they exhibit stereospecificity (+-amino acids are preferentially transported), broad substrate specificity (each transporter carries multiple different amino acids), and overlapping specificity (amino acids have access to multiple transporters) (4). Thus, amino acid transporters have been defined by these two main functional criteria: type of amino acid transported (acidic, neutral or zwitterionic, or basic) and transport mechanism used (facilitated diffusion or secondary active transport). Table 3

### Table 2. Characteristics of gastric, intestinal, and pancreatic peptidases

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Activators</th>
<th>Action</th>
<th>Cleavage Points</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pepsin</td>
<td>Autoactivation</td>
<td>Endopeptidase</td>
<td>Tyr, Phe, Leu, and Asp</td>
<td>Large peptide fragments and free amino acids</td>
</tr>
<tr>
<td>Trypsin</td>
<td>Enteropeptidase and trypsin</td>
<td>Endopeptidase</td>
<td>Arg and Lys</td>
<td>Oligopeptides (2-6 amino acids)</td>
</tr>
<tr>
<td>Chymotrypsin</td>
<td>Trypsin</td>
<td>Endopeptidase</td>
<td>Tyr, Trp, Phe, Met, and Leu</td>
<td>Oligopeptides (2-6 amino acids)</td>
</tr>
<tr>
<td>Elastase</td>
<td>Trypsin</td>
<td>Endopeptidase</td>
<td>Ala, Gly, and Ser</td>
<td>Oligopeptides (2-6 amino acids)</td>
</tr>
<tr>
<td>Carboxypeptidase A</td>
<td>Trypsin</td>
<td>Exopeptidase</td>
<td>Carboxy-terminus Val, Leu, Ile, and Ala</td>
<td>Free amino acids</td>
</tr>
<tr>
<td>Carboxypeptidase B</td>
<td>Trypsin</td>
<td>Exopeptidase</td>
<td>Carboxy-terminus Arg and Lys</td>
<td>Free amino acids</td>
</tr>
<tr>
<td>Aminopeptidases</td>
<td></td>
<td></td>
<td></td>
<td>Free amino acids</td>
</tr>
</tbody>
</table>

[Modified from Refs. 3, 4, and 6.]

### Table 3. Common amino acid and peptide transporters in intestinal epithelial cells

<table>
<thead>
<tr>
<th>Transport System</th>
<th>Amino Acid Substrates</th>
<th>Cotransported Ions</th>
<th>Type of Transport</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Neutral</td>
<td>Na⁺</td>
<td>Secondary active</td>
<td>Apical</td>
</tr>
<tr>
<td>B⁹⁺</td>
<td>Neutral, basic, and cystine</td>
<td>Na⁺</td>
<td>Secondary active</td>
<td>Apical</td>
</tr>
<tr>
<td>B⁺⁺</td>
<td>Neutral, basic, and cystine</td>
<td>None</td>
<td>Exchanging</td>
<td>Apical</td>
</tr>
<tr>
<td>Y⁺</td>
<td>Basic</td>
<td>None</td>
<td>Facilitated</td>
<td>Apical</td>
</tr>
<tr>
<td>Imino</td>
<td>Imino</td>
<td>Na⁺ and Cl⁻</td>
<td>Secondary active</td>
<td>Apical</td>
</tr>
<tr>
<td>Xₐg⁻</td>
<td>Acidic</td>
<td>Na⁺, H⁺, and K⁺</td>
<td>Secondary active</td>
<td>Apical</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>Na⁺ and Cl⁻</td>
<td>Secondary active</td>
<td>Apical</td>
</tr>
<tr>
<td>PAT1</td>
<td>Imino</td>
<td>H⁺</td>
<td>Secondary active</td>
<td>Apical</td>
</tr>
<tr>
<td>A</td>
<td>Neutral and imino</td>
<td>Na⁺</td>
<td>Secondary active</td>
<td>Basolateral</td>
</tr>
<tr>
<td>ASC</td>
<td>Neutral with 3-4 carbons</td>
<td>Na⁺</td>
<td>Exchanging</td>
<td>Basolateral</td>
</tr>
<tr>
<td>Asc</td>
<td>Neutral with 3-4 carbons</td>
<td>None</td>
<td>Facilitated</td>
<td>Basolateral</td>
</tr>
<tr>
<td>L</td>
<td>Neutral, large, and hydrophobic</td>
<td>None</td>
<td>Facilitated</td>
<td>Basolateral</td>
</tr>
<tr>
<td>y⁻</td>
<td>Basic</td>
<td>None</td>
<td>Facilitated</td>
<td>Basolateral</td>
</tr>
<tr>
<td>PEPT1</td>
<td>Oligopeptides</td>
<td>H⁺</td>
<td>Secondary active</td>
<td>Apical</td>
</tr>
</tbody>
</table>

[Modified from Refs. 3, 4, and 6.]
shows a summary of common transporters for amino acids and oligopeptides, their cotransported ions (if any), the type of transport, and their location in enterocytes. Neutral L-amino acids are absorbed across intestinal epithelial cells by entering via a secondary active Na\(^+\)-dependent cotransporter (known as system B) and exiting via a Na\(^+\)-independent facilitated diffusion transporter (4). Of the six other amino acid transporters found in the apical membranes of epithelial cells, some transport anionic (acidic), cationic (basic), and \(\beta\)-amino acids and some transport imino acids (4). Identifying the specific transporters found in specific locations in the small intestine for amino acid uptake has been difficult due to species differences.

Several loss-of-function mutations in amino acid transporters have been characterized based on the expression of similar transporters in small intestinal epithelial cells and renal proximal tubule cells (4). Loss of functional transporters in the kidney tubules results in easily measured amino acid excretion in the urine. In addition, the importance of di- and tripeptide transporters for absorption was discovered when a loss of the major neutral amino acid transporter did not lead to the expected deficiency of the neutral amino acids in the blood. This situation implied that some other type of transporter must be mediating uptake of the neutral amino acids from the intestinal lumen and helped lead to the discovery of di/tripeptide

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![Protein Digestion and Absorption Diagram](image-url)
transporter (PEPT1), the major intestinal transporter for the absorption of the di- and tripeptide products of digestion (6).

The H⁺-coupled di- and tripeptide cotransporters take advantage of a H⁺ electrochemical gradient from the lumen to the cytoplasm across the brush-border membranes of enterocytes (14). The intracellular pH of the enterocyte is 7.0–7.2, whereas the pH of the unstirred water layer that bathes the brush border is ~6.0, indicating a 10-fold concentration difference for protons. This electrochemical H⁺ gradient is generated and maintained by the Na⁺/H⁺ exchangers in the brush-border membranes coupled with the removal of Na⁺ from the cells across the basolateral membranes by Na⁺,K⁺-ATPases. The oligopeptide transporter family includes PEPT1 (found primarily in the small intestine and kidneys) and PEPT2.

Fig. 4. Summary of the basic steps involved in triglyceride digestion and absorption with important enzymes and transporters. The steps are explained in more detail in the text. FATP, fatty acid transport proteins. [Modified from Ref. 13.]
The blood. These transporters are likely Na+/H+ exchange transporters that are likely the predominant intestinal oligopeptide transporter and is found primarily in the duodenum and jejunum. PEPT1 is a low-affinity, high-capacity transport system with broad substrate specificity and appears to be involved in the uptake of most of the potential 400 dipeptides and 8,000 tripeptides resulting from the partial digestion of combining the 20 different amino acids into peptides.

PEPT1 is a 707-amino acid protein with 12 transmembrane-spanning domains that is likely the predominant intestinal oligopeptide transporter and is found primarily in the duodenum and jejunum. PEPT1 is a low-affinity, high-capacity transport system with broad substrate specificity and appears to be involved in the uptake of most of the potential 400 dipeptides and 8,000 tripeptides resulting from the partial digestion of combining the 20 different amino acids into peptides.

Indications for amino acids. Three transporters have been shown to transport amino acids bidirectionally. The alternative oligopeptide cotransporter can compensate for the absence of these individual apical amino acid transport systems and that the basolateral transporters for the amino acids are unaffected. In addition, the concomitant defects in transporters in kidney tubule cells leads to higher levels of amino acids in the urine.

Digestion and Absorption of Lipids

Currently in the United States, 30–40% of the calories in a typical Western diet come from fat, and >90% of the ingested fat is in the form of triglycerides. Dietary fatty acids found in food are long-chain fatty acids with >12 carbons (usually 16–20 carbons) known as C16, C18, and C20 long-chain fatty acids. Medium-chain fatty acids (C8–C12) are rarely found in food (except for coconuts) and are thus less important for digestion and absorption in humans. While short-chain fatty acids (C2, C3, and C4) are the major anions found in the stool, they are not found in food (H. J. Binder, personal communications). They result from the digestion of fats by the bacteria in the colon and thus often contribute to diarrhea by providing an osmotic gradient. Digestion of lipids can begin in the mouth with lingual lipase and gastric lipase (found in the kidneys but not in the small intestine). PEPT1 is a 707-amino acid protein with 12 transmembrane-spanning domains that is likely the predominant intestinal oligopeptide transporter and is found primarily in the duodenum and jejunum. PEPT1 is a low-affinity, high-capacity transport system with broad substrate specificity and appears to be involved in the uptake of most of the potential 400 dipeptides and 8,000 tripeptides resulting from the partial digestion of combining the 20 different amino acids into peptides.

Clinical examples. Two autosomal recessive disorders of amino acid transport across the apical membrane have given extensive insights into the absorption of amino acids and oligopeptides. Hartnup disease was first discovered in the Hartnup family and presents as defective intestinal and renal transport of neutral amino acids involving system B transporters. Hartnup disease is most often seen in children, who ultimately exhibit pellagra-like skin changes, cerebellar ataxia, and psychiatric abnormalities. A similar disorder, cystinuria, results in the abnormal absorption of cationic amino acids by system B0/H+ with normal absorption of neutral amino acids. Patients with cystinuria usually present with kidney stones made of cystine that may lodge in the ureter, causing genitourinary bleeding and severe pain. Neither of these conditions involves the oligopeptide cotransporter, and patients rarely exhibit protein deficiencies, indicating that the alternative oligopeptide cotransporter can compensate for the absence of these individual apical amino acid transport systems and that the basolateral transporters for the amino acids are unaffected. In addition, the concomitant defects in transporters in kidney tubule cells leads to higher levels of amino acids in the urine.
produced by chief cells. However, in adult humans, most fat arrives in the duodenum intact as only ~15% of fat digestion occurs by the time the food leaves the stomach (4).

The presence of fat in the duodenum leads to the stimulation of pancreatic enzyme secretion (including lipases and esterases) and contraction of the gallbladder with relaxation of the hepatopancreatic sphincter to release bile. The bile and pancreatic enzymes both enter the small intestinal lumen through the hepatopancreatic sphincter in the upper part of the duodenum. Emulsification of dietary fat is facilitated by cooking the food, continues with chewing, and finishes in the stomach with churning and peristalsis (10). Hydrolysis starts in the stomach with gastric lipase cleaving 15–20% of the fatty acids and is completed in the duodenum by lipases found in pancreatic juice (10). The emulsion is stabilized by preventing the dispersed lipid particles from coalescing again by coating them with bile salts, phospholipids, and cholesterol (4). Since digestive lipases have adapted to being more efficient at oil-water interfaces, turning dietary fat into an emulsion of fine oil droplets enhances the action of lipases (4). The smaller fat globules have an increased surface area and are more easily accessible to active pancreatic enzymes for further breakdown.

The emulsion droplets arriving from the stomach contain almost all of the dietary triglycerides and diglycerides in their cores and are covered by polar lipids, phospholipids, fatty acids, cholesterol, triglycerides, denatured dietary proteins, dietary oligosaccharides, and bile salts in the duodenum (10). The lipolysis proceeds from the outside in, and the interface continues to change as products form and leave the interface. During hydrolysis, emulsion droplets dissociate into multilamellar liquid crystals, which are converted into unilamellar vesicles by bile salts and into mixed micelles by the further addition of bile salts (4).

Although pancreatic lipase is secreted in its active form, pancreatic colipase is needed to facilitate digestion. Pancreatic colipase is secreted as procolipase and is activated by trypsin. Colipase likely binds to the dietary fat and to lipase to allow the triglyceride to enter the active site of the lipase enzyme to be hydrolyzed (10). Colipase also prevents the inactivation of lipase by the bile salts. Pancreatic lipase hydrolyzes fatty acids at positions 1 and 3 of the glycerol moiety and produces free fatty acids and a 2-monoglyceride (also known as a monoacylglyceride). Likewise, fatty acids are removed from dietary cholesterol by the bile salts. Pancreatic lipase hydrolyzes fatty acids at positions 1 and 3 of the glycerol moiety and produces free fatty acids and a 2-monoglyceride (also known as a monoacylglyceride). Since digestive lipases have adapted to being more efficient at oil-water interfaces, turning dietary fat into an emulsion of fine oil droplets enhances the action of lipases (4). The smaller fat globules have an increased surface area and are more easily accessible to active pancreatic enzymes for further breakdown.

The lipid-soluble breakdown products of dietary fats solubilized by bile salts inside mixed micelles (composed of bile salts and mixed lipids like fatty acids, monoglycerides, lyso-phospholipids, and cholesterol) are delivered across the unstimulated water layer bathing the brush-border membranes of the enterocytes. The mixed micelles reach the lipid bilayer of the enterocytes (the low-pH area generated by the previously described Na+/H+ exchangers in the brush-border membranes) (4). There, the fatty acids become protonated and leave the mixed micelles to either diffuse across the lipid bilayer membranes or temporarily become a cell membrane lipid. In contrast, amphipathic medium-chain free fatty acids (C4–C12), which are readily soluble in water, easily cross the unstirred water layer before uptake into the enterocytes through the lipid bilayer (4). Enterocytes do not reesterify the medium-chain fatty acids and transfer them directly into the portal blood to be transported to the liver bound to serum albumin. Although short-chain fatty acids are both water and lipid soluble, they are not absorbed in the small intestine. Short-chain fatty acids are not found in food and thus appear in the digestive tract only after the bacterial break down of undigested fats in the colon, leading to their synthesis and absorption almost exclusively in the colon (H. J. Binder, personal communications). The bile salts from the mixed micelles remain in the intestinal lumen and are later absorbed in the terminal ileum by a Na+-dependent active transport process to be recycled via the enterohepatic circulation. Figure 4 shows a summary diagram of the steps involved in the digestion and absorption of triglycerides.

![Image](http://advan.physiology.org.org/...)

**Fig. 6.** Summary of current insights into the formation of chylomicrons in enterocytes. The process begins in the rough endoplasmic reticulum (RER) as apolipoprotein B48 (apoB48) is charged by microsomal triglyceride transfer protein (MTP) to form stable complexes with dense particles (DP, phospholipids, cholesterol, and small amounts of triglycerides) if present. In the smooth endoplasmic reticulum (SER), a large light particle (LP) is formed with the merger of apoprotein AIV (apoAIV) and neutral lipids (orange). The chylomicron precursors merge in the SER to form lipid particles with neutral lipid cores and the two apoproteins, which buds from the SER surrounded by a membrane into a prechylomicron transport vesicle (PCTV). The PCTV fuses with the Golgi complex, where apoprotein AI (apoAI; from the SER with different transport vesicle) attaches to the prechylomicron to from a mature chylomicron. The mature chylomicrons exit the Golgi complex in large transport vesicles containing multiple chylomicrons for exocytosis across the basolateral membrane. Nuc, nucleus. [Used with permission from Ref. 11.]

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Traditionally, it was assumed that all of the breakdown products of lipid digestion entered enterocytes across the apical membrane by simple diffusion through the lipid bilayer. However, recently, both a protein-independent diffusion model and protein-dependent mechanisms have been proposed (11). Fatty acid translocase (FAT; known as FAT/CD36) appears to play a key role in the uptake of long-chain fatty acids in the small intestine with higher levels found in the proximal intestinal mucosa. Fatty acid uptake by cells has been shown to be saturable and competitive with other fatty acids. FAT/CD36 is highly expressed and is upregulated in the presence of dietary fat, genetic obesity, and diabetes mellitus (7). In addition, fatty acid transport proteins (FATP2–FATP4) are expressed in the small intestine (11) and are promising candidates for cellular long-chain fatty acid transporters that facilitate the uptake of fatty acids into the enterocytes (7). However, FATP4 (the form predominantly expressed in the small intestine) has recently been localized in the intestinal endoplasmic reticulum and shown to have CoA acylase function. Thus, the correlation of fatty acid uptake with FATP4 expression may be due to intracellular trapping of fatty acids as acyl CoA instead of enhanced apical transport of fatty acids (11). A third fatty acid-binding protein (FABP) in the plasma membrane (FABPpm) has also been found in the brush-border membranes of enterocytes and may play a role in fatty acid uptake (11). A transporter-facilitated mechanism is also likely involved in the uptake of cholesterol by enterocytes (7). Niemann-Pick C1-like 1 (NPC1L1) has been identified as a cholesterol uptake transporter, and two ATP-binding cassette proteins (ABCG5 and ABCG8) have been identified as cholesterol efflux transporters (7).

The breakdown products of triglyceride hydrolysis, which enter the intestinal epithelial cells across the apical membranes, cross the cytoplasm to the smooth endoplasmic reticulum to be reconstituted into complex lipids (7). Specific FABPs carry cytoplasmic fatty acids and monoglycerides to the intracellular sites, where several enzymes reassemble the fatty acids and monoacylglycerides to reconstitute triglycerides. The details for the formation of the reconstituted contents of the future chylomicrons are shown in Fig. 5.

Subsequently, the enterocytes package the reconstituted triglycerides with proteins and phospholipids into chylomicrons. A key structural component of chylomicrons is apoprotein B48 (ApoB48), a large, hydrophobic, nonexchangeable protein of the rough endoplasmic reticulum membrane (for details on the formation of the chylomicron, see Fig. 6) (7). The synthesis of chylomicrons is dependent on microsomal triglyceride transport protein (MTP), which catalyzes the transfer of the water-insoluble triglyceride to the enlarging lipid droplet and combines with a high-density, protein-rich particle in the rough endoplasmic reticulum. Subsequently, the ApoB48 and dense particle complex combines with a large light particle with attached apoprotein AIV from the smooth endoplasmic reticulum to form a prechylomicron (11). This prechylomicron may be included in a transport vesicle (prechylomicron transport vesicle), which buds off of the endoplasmic reticulum membrane and is transported to the Golgi apparatus for completion. The chylomicron uses a large second transport vesicle containing several chylomicrons to traverse from the Golgi to the basolateral membrane for exocytosis. Chylomicrons are exocytosed intact across the basolateral membranes to enter the central lacteal lymph vessels in the core of the villus and then enter the bloodstream later via the thoracic duct.

Case example. ApoB48 is used by enterocytes in the assembly of chylomicrons. ApoB48 serves as an acceptor for newly synthesized triglycerides being transferred by MTP, which is necessary to transfer triglycerides formed in the endoplasmic reticulum. Mutations in the gene for MTP are the basis for A-β-lipoproteinemia, which is characterized by the absence of intestinal lipoproteins in plasma. The symptoms of the disease include fat malabsorption or steatorrhea (high fat levels in feces). These patients may also show symptoms of deficiencies of lipid-soluble vitamins (6, 9).

Summary

A basic understanding of new details in the digestion and absorption of carbohydrates, proteins, and fats both provides fascination with the intricacy and integrates biochemical and physiological concepts. Insights into how the various enzymes work, how transport occurs across enterocytes, and disease conditions that interfere with the normal uptake and processing of food can help explain nutrition to normal, healthy individuals. Curiosity about these processes may help individuals to critically evaluate claims of companies trying to market nutritional supplements.

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DISCLOSURES

No conflicts of interest are declared by the author.

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