

Carbohydrate Digestion and Absorption
NASPGHAN Physiology Series

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Overview:

Carbohydrates in the diet provide the major exogenous source for glucose, which is the primary energy source for cells. They account for 40-60% of the calories in the western diet and higher percentages in protein scarce diets. Each gram of carbohydrate provides 4 calories.

Carbohydrates are hydrophilic and require a series of reactions to digest them to monosaccharides which are absorbed in the small intestine. Carbohydrates consist of three main groups, simple carbohydrates (monosaccharides), disaccharides and complex carbohydrates (starch, glycogen, and fiber). The common monosaccharides include glucose, fructose, galactose, xylose and ribose. The varying molecular arrangements result in varying degrees of sweetness, with fructose being the sweetest. Disaccharides are created by the condensation of two monosaccharides and require hydrolysis for separation at the time of absorption. Examples of disaccharides include - lactose (glucose and galactose), sucrose (glucose and fructose) and maltose (glucose and glucose). Complex carbohydrates include starch (amylose and amylopectin), fiber, glycogen (straight and branched chains of glucose), and glycolipids.

Digestion:

The goal of carbohydrate digestion is to break down all disaccharides and complex carbohydrates into monosaccharides for absorption, although not all are completely absorbed in the small intestine (e.g., fiber). Digestion begins in the mouth with salivary amylase released during the process of chewing. There is a positive feedback loop resulting in increased oral amylase secretion in people consuming diets high in carbohydrates. The amylase is synthesized in the serous cells of the salivary glands. Amylase breaks starches into maltose and polysaccharides. Amylase is sensitive to pH and thus is inhibited in the acidic environment of the stomach. Only 5% of starch is broken down by salivary amylase due to limited exposure. Salivary amylase has increased importance in two groups; infants with decreased pancreatic amylase production in the first 9 months and children with pancreatic insufficiency from cystic fibrosis or other etiologies.

Minimal carbohydrate digestion occurs in the stomach due to the inactivation of amylase in the acidic environment. Pancreatic amylase is released from acinar cells into the small intestine in concert with other enzymes under the stimulus of secretin and CCK and continues the process of carbohydrate digestion. Amylase targets the α -1,4 bonds of complex carbohydrates and is unable to break terminal bonds or α -1,6 bonds. Starch is digested in the small intestine to simple components derived from branched amylopectin (maltose, maltotriose and α -limit dextrins). Oligosaccharides and disaccharides are digested by specific enzymes in the microvillus membrane (brush border).

Brush border enzymes are synthesized in the endoplasmic reticulum and glycosylated in the Golgi apparatus of the enterocyte. They are then trafficked to the apical membrane where they are anchored at the surface by a transmembrane segment. The anchored enzymes are active following cleavage of a small residue at the extracellular N-terminal end. Disaccharidases are protected from proteolysis by glycosylation and are found in higher concentration in villus enterocytes of the proximal small bowel. These enzymes include maltase (digests maltose to glucose and glucose), sucrase (digests sucrose to fructose and glucose), trehalase (digests trehalose to glucose and glucose), lactase (digests lactose to galactose and glucose) and isomaltase (de-branching enzyme digests α 1,6 bonds of limit dextrin to produce glucose). Glucose does not require any additional digestion. The rate limiting step for absorption differs among the carbohydrates. Sucrose uptake is regulated after hydrolysis by the apical membrane uptake rate of fructose and glucose, whereas lactose absorption is limited by the rate of hydrolysis. (See Figure 2)

Humans born full-term have a full complement of disaccharidases at delivery. However, disaccharidase levels vary during gestation: sucrase appears early (by about 20 weeks), while lactase does not achieve “normal” levels until the 3rd trimester. In most humans, lactase decreases with age starting at about 3-5 years or earlier depending on the population. This pattern has been termed lactase non-persistence. However, in people of Northern European ancestry and other population groups in small areas elsewhere in the world, lactase activity remains at the infantile level. This is termed lactase persistence. Lactase non-persistence is found in the United States mainly in African-Americans, Asians, and Native Americans, although people of Southern European ancestry can also exhibit lactase non-persistence. Lactase activity is “hard wired” genetically; lactase is not inducible, and lactose restriction does not lower lactase levels. Carbohydrates not digested in the small intestine pass into the large intestine where they are digested by colonic bacteria. This results in the release of short chain fatty acids (SCFA) (propionate, butyrate and acetate) along with methane. The SCFA provide vital nutrition to colonocytes, but excess volumes induce diarrhea and abdominal cramping.

Clinical correlation - Disaccharide deficiency results in symptoms due to an increased osmotic load in the small intestine and frequently elevated short chain fatty acid (SCFA) production in the colon. The presence of SCFA and their contribution to colonocyte health must also be remembered in children with diversion colitis, which is due to an absence of SCFA.

Absorption:

Once carbohydrates are digested, the products must be absorbed and transported to the portal circulation. Digestion and absorption are typically coupled, with the enzymes closely located to the appropriate transporters. Glucose absorption occurs in the small intestine via the SGLT-1 transporter (sodium glucose co-transporter). Fructose absorption is completed via the GLUT5 transporter by facilitated diffusion. (See Figure 3)

Glucose and galactose are actively transported from the small intestine lumen by the sodium glucose transporter (SGLT-1) located in the brush border of the small intestine. The transporter is more prevalent in the duodenum and jejunum. Glucose transport is driven by a sodium gradient across the apical cell membrane generated by the Na^+, K^+ -ATPase pump located in the

basolateral membrane of the enterocyte. The Na^+, K^+ -ATPase pump creates a low intracellular sodium concentration by transporting 3 Na^+ ions out of the cell and 2 K^+ ions into the cell. The SGLT-1 transporter utilizes the sodium gradient. Two Na^+ ions bind to the outer face of the SGLT-1 transporter which results in a conformational change permitting subsequent glucose binding. The two Na^+ ions and the glucose molecule are then transferred to the cytoplasmic side of the membrane following another conformational change that involves rotation of the receptor. The glucose is released first followed by the sodium ions. The sodium is transported from high to low concentration (with concentration gradient) and at the same time allows the carrier to transport glucose against its concentration gradient. The Na^+ ion is subsequently expelled by Na^+, K^+ -ATPase pump to maintain the gradient. The SGLT-1 transporter undergoes another conformational change resulting in the binding sites again being exposed at the apical surface. This action can occur one thousand times per second. Much of the glucose transported into the cell passes out of the cell at basolateral surface by facilitated diffusion via GLUT-2. Sodium ions and accompanying anions and water follow the glucose, maintaining iso-osmolarity. A small portion of the glucose is utilized by the cell.

Facilitated diffusion is the mechanism for fructose transport. Facilitated diffusion utilizes a carrier protein to achieve transport at rates greater than simple diffusion and does not rely on concentration gradients. GLUT-5 is present on the apical membrane of the brush border throughout the small intestine with increased density in the proximal small intestine. Little fructose is metabolized in the cell. Both GLUT-2 and GLUT-5 are present at the basolateral membrane to transport fructose to the portal circulation. Fructose malabsorption can be minimized by simultaneous glucose administration suggesting there is another glucose responsive system in the enterocytes.

There continues to be debate about passive glucose absorption. Recent data suggests passive glucose absorption does exist, but that it is a facilitated system mediated by glucose-dependent activation. The GLUT-2 facilitative glucose transporter can be recruited to the brush border membrane to assist with glucose transport.

Disaccharidase Regulation

Sucrase-isomaltase (SI) and maltase-glucoamylase levels increase in response to high carbohydrate intake, suggesting a transcriptional regulation mechanism. SI is encoded for by a gene located on chromosome 3. The 5' flanking region of the SI gene has several DNA regulatory regions that control the initiation of gene transcription. Three different transcriptional proteins are involved in SI transcription promotion including; hepatocyte nuclear factor (HNF-1), GATA-type zinc finger transcription factors, and caudal-related homeodomain proteins (Cdx). There are also promoter regions that down-regulate SI transcription. Down regulation of SI occurs in the presence of glucose. Hormonal influences have also been proposed and are currently being studied further.

Unlike SI, lactase production is not affected by diet. The lactase gene is located on chromosome 2. Studies have demonstrated that Cdx, HNF-1 and GATA 5, along with other transcription factors all interact with the proximal promoter region and result in transcription initiation. A distal promoter region has been identified and is currently being characterized. It has also been

proposed that a repressor region exists that down regulates lactase expression. It has been hypothesized that lactase persistent people fail to bind this repressor due to single nucleotide polymorphisms (SNPs) These SNPs are currently under investigation.

Clinical Correlations:

- Lactose Intolerance
 - See above for lactose intolerance clinical presentation and natural history
 - Management of lactose intolerance per the 2010 NIH Consensus Guidelines (<http://consensus.nih.gov/2010/lactosestatement.htm>)
 - Limit lactose to 12 grams (approx. 1 cup) and titrate for symptoms
 - Recommend lactose be taken with other foods
 - Evaluate diet for adequate nutrition, particularly calcium and Vitamin D
 - Studies are currently lacking to support use of probiotics or supplemental lactase.
- Congenital Sucrase-Isomaltase Deficiency
 - Autosomal recessive disease due to homozygous or heterozygous mutations in the SI gene resulting in maldigestion of sucrose. Found in 1 in 5,000 North Americans, but more significant in Arctic indigenous peoples with 10% of Eskimos affected. Presents with osmotic diarrhea, abdominal pain and FTT. Treatment requires dietary elimination of sucrose and occasionally initially a starch free diet. Once the child is sucrose free, starch may be slowly reintroduced. There is a supplement for sucrase, Sucraid[®], available.
- Small Bowel Bacterial Overgrowth
 - Increased bacteria in the small bowel due to dysmotility, infection or medication exposures. The bacteria present in SBBO result in increased fermentation of sugars. Diagnosis may be made by clinical history and supported by breath testing, although the sensitivity and specificity of this test is approximately 60%. In this test, malabsorption of the test sugar results in increased breath H⁺.
- Pancreatic Insufficiency
 - May be due to cystic fibrosis, chronic pancreatitis, or pancreatic duct obstruction (tumor). Due to decreased enzyme release there is inadequate carbohydrate digestion resulting in malabsorption. Only 10% of baseline quantities of amylase are needed to avoid symptoms of malabsorption. Failure to alkalinize fluid in small intestine and therefore inactivation of the pancreatic enzymes may also result in functional pancreatic insufficiency; this may occur when there is villus atrophy as in celiac disease. The cause is inadequate release of secretin and CCK.
- Celiac disease
 - Due to decreased absorptive capacity (decreased number of transporters) and decreased brush border enzymes associated with decreased villus length there

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is inadequate digestion and absorption of carbohydrates. Once a gluten free diet produces mucosal healing, disaccharidase deficiency abates.

Glucose-Galactose Malabsorption

—A very rare mutation of SGLT-1 results in a defective transporter that presents with severe diarrhea at birth. The diarrhea is osmotic in nature due to glucose and galactose malabsorption. Infants present with diarrhea, FTT and malnutrition. Treatment is fructose containing formula and avoidance of glucose and galactose.

Additional Reading:

1. Barrett K. Carbohydrate, Protein and Water-Soluble Vitamin Assimilation. In GI Physiology. 2nd ed. New York, NY. McGraw Hill, 2013: 256-284
2. Montgomery RM, Krasinski SD, Hirschorn JN, Grand RJ. Lactose and Lactase – Who is Lactose Intolerant and Why? J Pediatr Gastroenterol Nutr 2007;45:S131-137.
3. Wright EM, Loo DDF, Hirayama BA. Physiol Rev 2011;91:733-794.

Review Questions:

1. A 9y.o Asian boy is brought to your office by his mother. They report that he has had worsening diarrhea for the past 6 months following a viral acute gastroenteritis. What is the most likely reason for his diarrhea?
 - a. Celiac disease
 - b. Lactose Non-persistence
 - c. Pancreatic Insufficiency
 - d. Infection

Answer: Lactose Intolerance

2. What enzymes involved in carbohydrate digestion are induced by increasing dietary intake?
 - a. Lactase
 - b. Sucrase-isomaltase
 - c. Maltase-glucoamylase
 - d. Amylase

Answer: Both B and C

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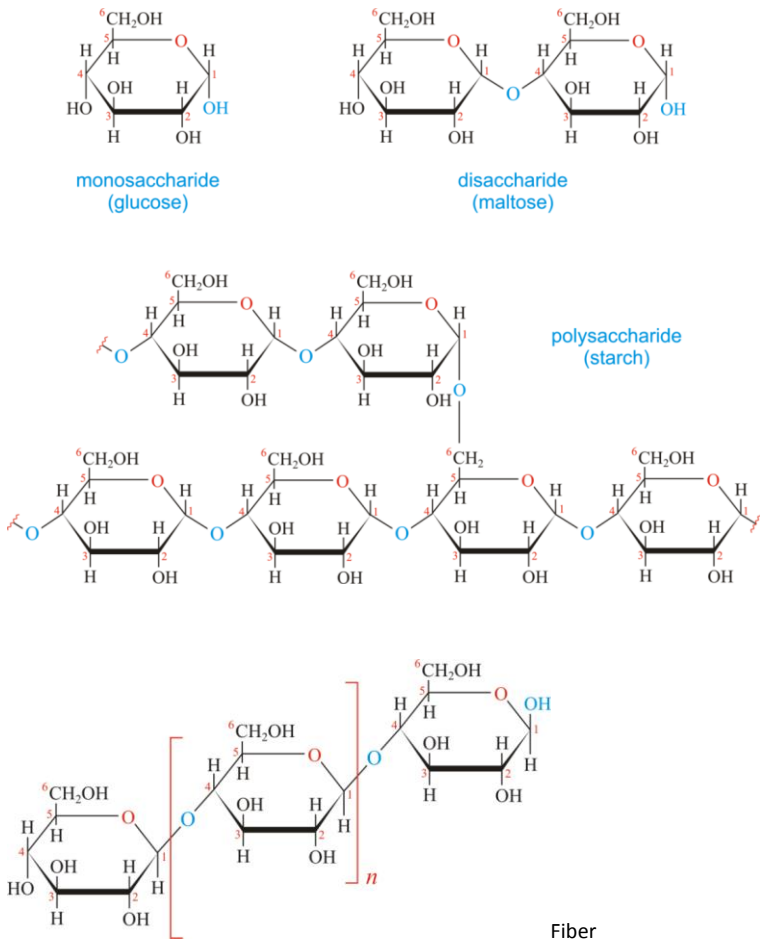


Figure 1. Carbohydrates consist of three main groups, simple carbohydrates (monosaccharides), disaccharides and complex carbohydrates (starch, fiber and glycogen).

Digestion

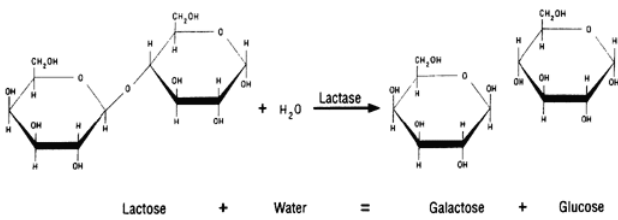
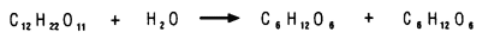
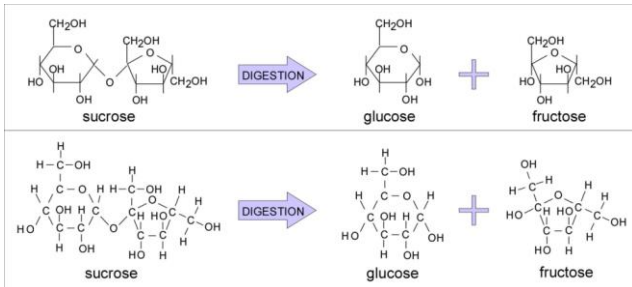
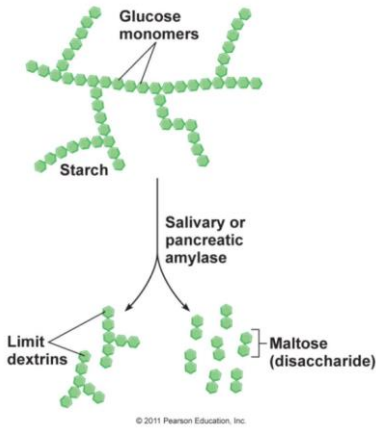


Figure 2. Carbohydrates are digested to monosaccharides for absorption and transport to the portal vein.

Absorption

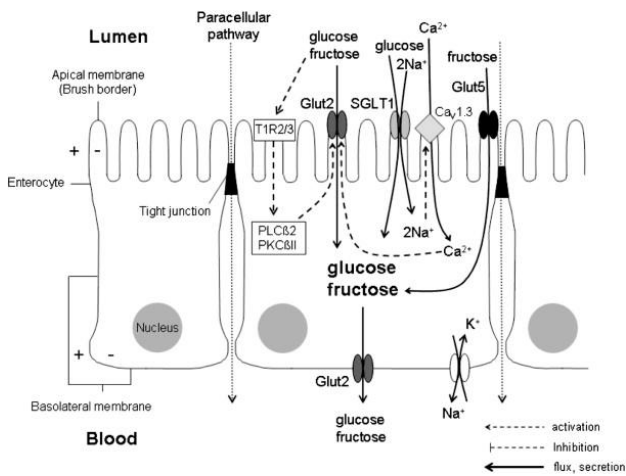
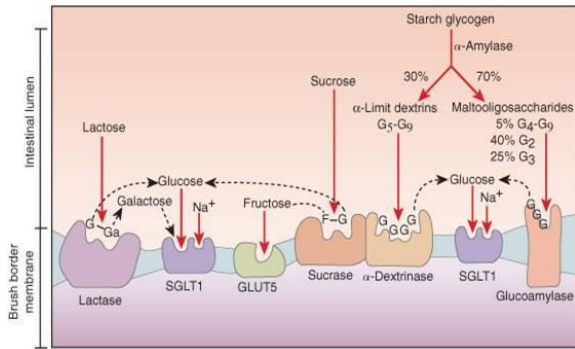


Figure 3. Digestion and absorption are typically coupled with the enzymes being closely located with the appropriate transporters. Glucose absorption occurs in the small intestine by active transport via the SGLT-1 transporter (sodium glucose co-transporter). Galactose, fructose and some glucose absorption is completed by the GLUT5 transporter by facilitated diffusion.