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M1 - GI Sequence

Intestines

John Williams, M.D., Ph.D.

Winter, 2009
THE SMALL INTESTINE

Human small intestine 6-7 m long
  Duodenum 20-30 cm
  Jejunum 2.5 m
  Ileum 3.5 m

FUNCTIONS
  Digestion
  Absorption
  Secretion
  Motility

Fig. 7-2 Granger, D, et al. Clinical Gastrointestinal Physiology. W.B. Saunders, Philadelphia, PA; 1985: 144.
Small Intestine Anatomy
Histologic organization of the small intestinal mucosa

## DIETARY CARBOHYDRATES

<table>
<thead>
<tr>
<th>POLYSACCHARIDES</th>
<th>DISACCHARIDES</th>
<th>MONOSACCHARIDES</th>
<th>INDIGESTIBLE CARBOHYDRATES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. STARCH</td>
<td>SUCROSE</td>
<td>FRUCTOSE</td>
<td></td>
</tr>
<tr>
<td>AMYLOSE</td>
<td>LACTOSE</td>
<td>GLUCOSE</td>
<td></td>
</tr>
<tr>
<td>AMYLOPECTIN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. GLYCOGEN</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Polysaccharides: 60%
- Disaccharides: 30%
- Monosaccharides: 0%
DIETARY CARBOHYDRATES (cont)

- Normal American diet contains 200-300 g (50% of caloric intake)
- Serves an energy and carbon source
- Digestion includes a luminal phase and a brush border phase
- Only monosaccharides are appreciably absorbed
Amylase (pH optima 7) cleaves interior α1-4 linkages but not α1-6.

Endproduct is a mixture of maltose, maltotriose and limit dextrans.

Acarbose – Amylase inhibitor

Starch = Amylose & Amylopectin
Intestinal Brush Border Phase of Carbohydrate Digestion

Structure of Sucrase-Isomaltase

Lumen

[Diagram showing the structure of Sucrase-Isomaltase with labeled components]

Cytosol of enterocyte

Intestinal Brush Border Hydrolysis of Oligosaccharides

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrates</th>
<th>Molecular Site of Hydrolysis</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maltase</td>
<td>Maltose, maltotriose</td>
<td>α-1,4 linkage</td>
<td>glucose</td>
</tr>
<tr>
<td>Sucrase*</td>
<td>Sucrose</td>
<td>α-1,4 linkage</td>
<td>glucose, fructose</td>
</tr>
<tr>
<td>Lactase</td>
<td>Lactose</td>
<td>β-1,4 linkage (but not of cellulose)</td>
<td>glucose, galactose</td>
</tr>
<tr>
<td>α-Dextrinase (isomaltase)</td>
<td>α-Limit dextrins</td>
<td>α-1,6 linkage</td>
<td>glucose, maltose, oligosaccharides</td>
</tr>
</tbody>
</table>

*Sucrase is also very active against maltose and maltotriose.
MECHANISM OF MONOSACCHARIDE ABSORPTION

Diagram showing the absorption of monosaccharides through the intestinal lining. Key components include:

- **Lumen**: Entry point for monosaccharides.
- **Cell**: Transport of monosaccharides into the cell.
- **Blood**: Translocation of monosaccharides from the cell to the bloodstream.

Key transporters and processes:

- **SGLT1**: Sodium-glucose cotransporter 1.
- **GLUT2**: Glucose transporter 2.
- **GLUT5**: Fructose transporter.
- **Na+/K+ pump**: Ion pump that transports sodium out and potassium in, essential for active transport.

Monosaccharides absorbed include:

- **Galactose/Glucose**
- **Fructose**

The diagram illustrates the mechanisms by which these monosaccharides are absorbed and transported across the intestinal epithelium.
Lactase is present in infancy and disappears to a variable extent during childhood in most humans.

Exception is Northern Europeans and European Americans—commonly retain lactase into adulthood.

Fig. 7-15 Granger, D, et al. Clinical Gastrointestinal Physiology. W.B. Saunders, Philadelphia, PA; 1985: 169.
DIETARY PROTEIN

• Normal humans require about 0.75 g/kg body weight of high quality dietary protein daily

• Nine essential amino acids are not synthesized and must be obtained from diet

• Normal American diet contains 70-90 g/day

Also endogenous protein in digestive secretions and shed epithelial cells
• Digestion includes a luminal and brush border phase

• Both amino acids and di- and tri-peptides absorbed

• Digestion normally quite complete
Activation of Pancreatic Proteolytic Enzymes

Precursors

1 6 Valine
7 Isoleucine
229

Active proteases

1 6 Valine
7 Isoleucine
229

Trypsinogen → Enterokinase → Trypsin

Chymotrypsinogen
Proelastase
Procarboxypeptidase A
Procarboxypeptidase B

Chymotrypsin
Elastase
Carboxypeptidase A
Carboxypeptidase B

Fig. 11-8 Johnson, L. Gastrointestinal Physiology, 7th ed. Mosby Elsevier, Philadelphia, PA; 2007: 114.
Luminal Phase of Protein Digestion

Endopeptidases

Exopeptidases

PROTEIN

Trypsin

Chymotrypsin

Elastase

PEPTIDES

BASIC (COOH-TERMINAL)

AROMATIC (COOH-TERMINAL)

ALIPHATIC (COOH-TERMINAL)

PEPTIDES

ARGinine

LYSINE

SMALL PEPTIDES

NEUTRAL AMINO ACIDS

carboxypeptidase B

carboxypeptidase A

Di & tri Peptides
H+ coupled PepT1

Peptidases ~20
Including enterokinase
Endo-; amino; carboxly etc

Small amounts of peptides enter blood intact- may be important in immune response

Protein Digestion
1 luminal (stomach, pancreas)
2 brush border (enterocyte)
3 intracellular (enterocyte)

Na+ coupled
Carrier to exit cell
Apical transporter
PepT1
Defects in Absorption of Protein Digestion Products due to Altered Transport Systems in Gut and Kidney

• Cystinuria
  Autosomal Recessive
  Increased excretion in urine with renal stones

• Hartnup Disease
  Autosomal Recessive
  Impaired absorption of neutral amino acids
  Symptoms of Niacin deficiency (Pellagra)

Patients normally don’t show protein malnutrition-di and tri peptides sufficient
DIETARY LIPID

• Normal American diet about 100g/day primarily as triglyceride

• Long chain “essential” polyunsaturated fatty acids, cholesterol, and fat soluble vitamins also present

• Lipid digestion begins in stomach and is completed in upper intestine in the lumen

• Multiple lipase enzymes have pH optima between 6 and 7
STEPS IN LIPID DIGESTION

1. Emulsification
   physical process takes place in stomach
   phospholipids, proteins facilitate

2. Digestion
   stomach and duodenum

3. Solubilization
   requires bile salts
   role of mixed micelles

4. Absorption
   normally <5gm in stool- more is “steatorrhea”
• pH optimum 6-7
• in presence of bile salts acid inactivates

Fig. 8 Johnson, L. *Essential Medical Physiology* New York Raven Press 1992: 515.
Colipase anchors lipase to the fat droplet in the presence of bile salts.

Mixed micelles solubilize the products of lipid digestion.
Ways to alter fat digestion and absorption

1. Olestra - Fake fat, can’t be digested

2. Orlistat (Xenical) – Covalent Lipase inhibitor
   Now available OTC as Alli

Side effect of both is malabsorption and diarrhea
Lipid Absorption in the Small Intestine
Short and medium chain fatty acids as well as glycerol
Medium Chain Triglycerides

1. Fatty acids are 6-12 carbons in chain length

2. Present in small amounts in normal diet

3. Can be digested and absorbed without bile salts due to increased water solubility

4. Fatty acids not reesterified but taken up into the portal vein
Cholesterol Absorption

• Luminal cholesterol comes largely from diet and bile; about 50% absorbed by intestine

• Cholesterol absorbed selectively as compared to plant sterols

• Absorbed cholesterol released in chylomicron and goes back to liver as chylomicron remnants

• Ezetimibe (Zetia) is a new drug that blocks cholesterol entry into the enterocyte
CALCIUM ABSORPTION

1. Dietary intake about 1000 mg/day with net absorption of about 100 mg/day

2. Most active in duodenum and involves an energy dependent, transcellular pathway

3. Regulated by active form of Vit D, 1,25(OH)$_2$ Vit D, also known as 1,25(OH)$_2$-cholecalciferol
Mechanism of Intestinal Calcium Absorption

Paracellular – Vit D-independent

Transcellular – Vit D-dependent

Fig. 9 Chang, E, Sitrin, M, Black, D. Gastrointestinal, Hepatobiliary, and Nutritional Physiology. Lippincott – Raven, Philadelphia, PA; 1996: 204.
MOLECULAR COMPONENTS OF INTESTINAL CALCIUM ABSORPTION

1. Entry across the apical brush border is mediated by a specific Ca\textsuperscript{2+} entry channel known as CaT1

2. Within the enterocyte a calcium binding protein, calbindin binds and transports Ca\textsuperscript{2+}

3. Ca\textsuperscript{2+} exit across the basolateral membrane is mediated by the plasma membrane Ca\textsuperscript{-2+}ATPase, PMCA1
Synthesis and Action of Vitamin D

Fig. 12-6 Johnson, L. Gastrointestinal Physiology, 7th ed. Mosby Elsevier, Philadelphia, PA; 2007: 133.
Primary Sites of Nutrient Absorption

Stomach
Lipophillic molecules (ethanol)
Weak acids (aspirin)
INTESTINAL ELECTROLYTE ABSORPTION AND SECRETION
Volumes and ionic composition of fluid entering the human intestine

<table>
<thead>
<tr>
<th>Segment</th>
<th>Vol (ml)</th>
<th>Na (mm)</th>
<th>K (mm)</th>
<th>Cl (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entering Duodenum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>2,000</td>
<td>150</td>
<td>50</td>
<td>200</td>
</tr>
<tr>
<td>Saliva</td>
<td>1,000</td>
<td>50</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Gastric juice</td>
<td>2,000</td>
<td>100</td>
<td>15</td>
<td>280</td>
</tr>
<tr>
<td>Bile</td>
<td>1,000</td>
<td>200</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>Pancreatic juice</td>
<td>2,000</td>
<td>150</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>Small intestinal secretion</td>
<td>1,000</td>
<td>150</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>9,000</td>
<td>800</td>
<td>100</td>
<td>700</td>
</tr>
<tr>
<td>Entering ileum</td>
<td>5,000</td>
<td>700</td>
<td>40</td>
<td>550</td>
</tr>
<tr>
<td>Entering colon</td>
<td>1,500</td>
<td>200</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>Stool</td>
<td>100</td>
<td>3</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>
DUODENAL FLUID DYNAMICS

• Mucosa is leaky allowing rapid osmotic equilibration of hypertonic and hypotonic meals

• Duodenal secretion of $\text{HCO}_3^-$ from Brunner’s glands

• Absorption by small intestine is then isotonic
Cellular Models of Intestinal Sodium Absorption

Can be regulated by contents, neurotransmitterers, inflammatory mediators and systemic hormones, particularly Angiotensin II

Fluid Absorption According to the Standing Osmotic Gradient Model

Can account for isotonic movement of fluid by use of localized hypertonicity.

Secretory diarrhea of Cholera is due to Cholera Toxin activating cAMP and stimulating secretion to 15–20 liters per day.
INDUCERS OF COLONIC AND SMALL INTESTINAL SECRETION

1. BACTERIAL ENDOTOXINS (CHOLERA)
2. CERTAIN UNSATURATED FATTY ACIDS (CASTOR OIL)
3. BILE ACIDS
4. ANTHRQUINONE CATHARTICS (SENNNA, CASCARA)
5. CERTAIN HORMONES (VIP)
INTESTINAL MOTILITY
FUNCTIONS OF INTESTINAL MOTILITY

1. Mixing of foodstuffs, digestive secretions and enzymes
2. Facilitate contact of chyme with intestinal mucosa
3. Net propulsion in an aboral direction
Intraluminal Pressure Changes in the Duodenum of a Conscious Man

In duodenum contractions occur at intervals of 5 sec or multiples of 5
Electrical Threshold for Generation of Action Potentials

Frequency of slow waves is 12/min in duodenum and decreases to 9/min in the ileum. (Another site of pacemaker activity)
ICC Cells
Interstitial Cells of Cahal

Source Undetermined
Fed pattern initiated by the Presence of chyme in the intestine.
Villus contraction which increases after a meal also helps mix unstirred layer and compress the lacteal.

Only very short peristaltic movements occur in the fed state.

Fig. 5-3 Johnson, L. Gastrointestinal Physiology, 7th ed. Mosby Elsevier, Philadelphia, PA; 2007: 44.
Migrating Motility Complex

phase III activity front
Relationship between Plasma Motilin and the MMC
MINERAL ABSORPTION
ESSENTIAL MINERAL ELEMENTS

1. Required to maintain normal physiology and health

2. Occur in diet, sometimes as trace elements

3. Variable absorptions may be regulated

4. In steady state intestinal absorption equals body losses
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Slide 10 – Source Undetermined

Slide 11 – John Williams

Slide 12 – Fig. 7-15 Granger, D, et al. *Clinical Gastrointestinal Physiology*. W.B. Saunders, Philadelphia, PA; 1985: 169.


Slide 17 – Source Undetermined

Slide 18 – Source Undetermined

Slide 22 – Fig. 8 Johnson, L. *Essential Medical Physiology* New York Raven Press 1992: 515.

Slide 23 – Source Undetermined

Slide 25 - Source Undetermined

Slide 26 – Fig. 11-14 Johnson, L. *Gastrointestinal Physiology*, 6th ed. Mosby Elsevier, St. Louis, MO; 2001: 136.

Slide 28 – Source Undetermined
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Slide 31 – Fig. 9 Chang, E, Sitrin, M, Black, D. Gastrointestinal, Hepatobiliary, and Nutritional Physiology. Lippincott – Raven, Philadelphia, PA; 1996: 204.
Slide 34 – John Williams
Slide 36 – Source Undetermined
Slide 40 – Source Undetermined
Slide 44 – Fig. 5-1 Johnson, L. Gastrointestinal Physiology, 7th ed. Mosby Elsevier, Philadelphia, PA; 2007: 42.
Slide 45 – Source Undetermined
Slide 46 – Source Undetermined
Slide 47 – Source Undetermined
Slide 48 – Fig. 5-3 Johnson, L. Gastrointestinal Physiology, 7th ed. Mosby Elsevier, Philadelphia, PA; 2007: 44.
Slide 49 – Jim Sherman
Slide 50 – Jim Sherman
Slide 51 – Source Undetermined