Mammalian Physiology

Gastrointestinal System: Digestion and Absorption
Objectives

• Describe the digestive secretions of the liver and pancreas
• Describe the digestion and absorption of carbohydrates
• Describe the digestion and absorption of proteins
• Describe the digestion and absorption of fats
Gastrointestinal Blood Flow

- All blood from gut, spleen, & pancreas flows directly into liver via portal vein
- Liver performs a filter function, metabolic processing, nutrient storage
- Blood leaves liver via hepatic veins which empty into vena cava and general circulation
Liver

• The largest gland in the body
• Hepatocytes’ functions include:
  – Production of bile
  – Processing blood borne nutrients
  – Storage of fat-soluble vitamins
  – Detoxification
• Secreted bile flows between hepatocytes toward the bile ducts in the portal triads (bile duct, hepatic artery, hepatic portal vein)
Digestive Secretions - Liver

- Secretion of bile (600-1000 mg/day)
- Bile is sequestered in gall bladder
- Function
  - Fat digestion and absorption
    - Emulsify large fat particles into small particles
    - Aid in absorption of digested fat end products
  - Pathway for excretion of waste products from the blood
    - Bilirubin
    - Cholesterol
The Gallbladder

- Thin-walled, green muscular sac on the ventral surface of the liver
- Stores and concentrates bile by absorbing its water and ions
- Releases bile via the cystic duct, which flows into the bile duct
Composition of Bile

- A yellow-green, alkaline solution containing bile salts, bile pigments, cholesterol, neutral fats, phospholipids, and electrolytes
- Bile salts are cholesterol derivatives that:
  - Emulsify fat
  - Facilitate fat and cholesterol absorption
  - Help solubilize cholesterol
- Enterohepatic circulation recycles bile salts
- The chief bile pigment is bilirubin, a waste product of heme
Regulation of Bile Release

• Acidic, fatty chyme causes the duodenum to release:
  – Cholecystokinin (CCK) and secretin into the bloodstream

• Bile salts and secretin transported in blood stimulate the liver to produce bile

• Vagal stimulation causes weak contractions of the gallbladder

• Cholecystokinin causes:
  – The gallbladder to contract
  – The hepatopancreatic sphincter to relax

• As a result, bile enters the duodenum
Digestive Secretions - Pancreas

- Pancreatic secretions contains enzymes for digesting all three major food types
- Stimuli for secretion include acetylcholine, cholecystokinen, secretin
- Pancreatic secretions
  - Proteolytic enzymes: trypsin, chymotrypsin
  - Pancreatic amylase
  - Pancreatic lipase, cholesterol esterase, phospholipase
  - Bicarbonate
Pancreas

Pancreas secretes about 2 L of fluid /day
Secretions contain digestive enzymes in an alkaline fluid which neutralizes acid chyme in duodenum – maintains optimum pH for digestive enzymes

Acinar cell
Same appearance as salivary acinar cell
- Elaborate rough endoplasmic reticulum
- Extensive Golgi apparatus
- Zymogen granules (enzyme containing secretory granules)
Secretes digestive enzymes

Duct cell
- Secretes bicarbonate
Pancreas

- **Exocrine function**
  - Secretes pancreatic juice which breaks down all categories of foodstuff
- The pancreas also has an endocrine function – release of insulin and glucagon

**Pancreatic Juice**

Water solution of enzymes and electrolytes (primarily HCO$_3^-$)
- Neutralizes acid chyme
- Provides optimal environment for pancreatic enzymes

Enzymes are released in inactive form and activated in the duodenum
Pancreatic Secretion

Cephalic phase – sensory stimulation stimulates enzyme release via vagus nerve

Gastric phase – distension of stomach activates vagovagal reflex and peptones stimulate G cells in antrum of stomach to release gastrin – stimulate release of digestive enzymes from acinar cells
Pancreatic Secretion

Intestinal phase – arrival of gastric acid stimulates S cells to release secretin which activates release of $\text{HCO}_3^-$ from duct cells

Lipids & proteins
1. stimulate I cells to release CCK
2. initiate a vagovagal reflex
Pancreatic Acinar Cell Secretions

- Synthesis of digestive enzymes is initiated on ribosomes on ER
- Enzymes are transported to ER cisternae, then to Golgi cisternae for incorporation into vesicles
- As vesicle density increases, they become zymogen granules
- When cell is stimulated, vesicles fuse with plasma membrane and granules are discharged
- Each zymogen granule contains several classes of digestive enzymes
Pancreatic Acinar Cells

Two second messenger pathways for release of enzymes

ACh and CCK stimulate zymogen granule release by IP3 – DAG pathway

Secretin & VIP stimulate release by adenylyl cyclase – cAMP pathway
Pancreatic Acinar Cells Secretion

Both ACh and CCK stimulate NaCl secretion

Pathway involves Na/K ATPase pump, NKCC transporter, electrochemical gradient for Cl\(^{-}\), Na\(^{+}\) transport via the paracellular pathway, H\(_{2}\)O transport via paracellular pathways and transmembrane water channels.
Pancreatic Acinar Cells

Monophasic response – classic dose response

Biphasic response – secretion reaches maximal level, then decreases with increasing concentration of secretagogue

Biphasic response suggests high and low affinity receptors

High affinity receptors stimulate, low affinity receptors inhibit secretion
Pancreatic Acinar Cells

Separate stimulatory pathways lead to additive effects

High affinity CCK receptor acts via $[Ca^{2+}]$ while VIP receptor acts via [cAMP]
Pancreatic Duct Cell Secretion

HCO₃⁻ secretion depends on exchange with Cl⁻

Cl⁻ recycles via membrane channels - cystic fibrosis transmembrane regulator (CFTR) & outward rectifying chloride channel (ORCC)

Secretin is most important secretagogue for HCO₃⁻: activates adenylyl cyclase, raises cAMP, stimulates pkA, and phosphorylates CFTR
The ionic composition of pancreatic secretions depends on secretory rate. Cl\(^-\) and HCO\(_3\)^- vary in reciprocal manner – HCO\(_3\)^- increases and Cl\(^-\) decreases with increased secretion rate.

HCO\(_3\)^- secretion depends on exchange with Cl\(^-\). Cl\(^-\) recycles via membrane channels.

Secretin is most important secretagogue for HCO\(_3\)^-.
Pancreatic Enzymes

Enteropeptidase (brush border enzyme in duodenum)

Trypsinogen $\rightarrow$ trypsin $\rightarrow$ trypsin $\rightarrow$ chymotrypsin $\rightarrow$ elastase $\rightarrow$ carboxypeptidase A $\rightarrow$ carboxypeptidase B

\{
  \text{endopeptidases}
\}

\{
  \text{exopeptidases}
\}

Trypsin produces digestive enzymes by cleaving respective proenzymes.
Endopeptidases cleave interior peptide bonds producing oligopeptides (2-6 amino acids).
Exopeptidases remove N- or C-terminal amino acids.
Regulation of Pancreatic Enzyme Secretion

Cholecystokinin released from small intestine stimulates release of pancreatic digestive enzymes.

Cephalic phase – sensory stimulation stimulates enzyme release via vagus nerve.

Intestinal phase – arrival of gastric acid stimulates S cells to release secretin which activates release of HCO$_3^-$ from duct cells.
Regulation of Pancreatic Secretion

- Secretin and CCK are released when fatty or acidic chyme enters the duodenum
- CCK and secretin enter the bloodstream
- Upon reaching the pancreas:
  - CCK induces the secretion of enzyme-rich pancreatic juice
  - Secretin causes secretion of bicarbonate-rich pancreatic juice
- Vagal stimulation also causes release of pancreatic juice
Structure of Small Intestine Villi

Epithelium lining intestine is not flat – surface area is increased by villi – finger like projections about 0.5 mm long. Apical surface is covered with a brush border of about 1,500 microvilli. Brush border contains enzymes and carrier proteins for absorption of monosaccharides and amino acids.

Fat is absorbed via lacteals – blind-ended lymphatic vessels. Other nutrients are absorbed via capillary network.
General Scheme of Absorption

Digestion-absorption can follow any of five patterns
Sites of Nutrient Absorption

CHO, protein, lipid absorbed along entire small intestine, although most in duodenum

Other nutrients absorbed preferentially in intestinal segments
Carbohydrate Digestion

- Absorption: via cotransport with $\text{Na}^+$, and facilitated diffusion
  - Enter the capillary bed in the villi
  - Transported to the liver via the hepatic portal vein
- Enzymes used: salivary amylase, pancreatic amylase, and brush border enzymes

End product of carbohydrate digestion is monosaccharides (glucose, galactose, mannose, fructose)
Important Monosaccharides

Figure 13-6. Epimerization of glucose.

α-D-Galactose  ↔  α-D-Glucose  ↔  α-D-Mannose

α-D-Fructofuranose
## Important Monosaccharides

<table>
<thead>
<tr>
<th>Sugar</th>
<th>Source</th>
<th>Importance</th>
</tr>
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<tbody>
<tr>
<td>D-Glucose</td>
<td>Fruit juices. Hydrolysis of starch, cane sugar, maltose, and lactose.</td>
<td>The &quot;sugar&quot; of the body. The sugar carried by the blood, and the principal one used by the tissues. Glucose is usually the &quot;sugar&quot; of the urine when glycosuria occurs.</td>
</tr>
<tr>
<td>D-Fructose</td>
<td>Fruit juices. Honey. Hydrolysis of cane sugar and of inulin (from the Jerusalem artichoke).</td>
<td>Can be changed to glucose in the liver and intestine and so used in the body.</td>
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<tr>
<td>D-Galactose</td>
<td>Hydrolysis of lactose.</td>
<td>Can be changed to glucose in the liver and metabolized. Synthesized in the mammary gland to make the lactose of milk. A constituent of glycolipids and glycoproteins.</td>
</tr>
</tbody>
</table>
Important Disaccharides

Maltose = glucose + glucose

Sucrose = glucose + fructose

Lactose = glucose + galactose
Carbohydrate Absorption

Dietary carbohydrates are mostly glucose polymers (60% starch & glycogen), and disaccharides (30% sucrose & 10% lactose) - $\alpha$-amylase splits internal 1-4$\alpha$ linkages to produce maltose.

Disaccharides are split into component monosaccharides by specific brush border enzymes – maltase, sucrase, lactase.
Carbohydrate Absorption

- Glucose and galactose are absorbed in a two step process
  - SGLT transporter – Na/glucose co-transport across apical membrane
  - GLUT 2 transporter – transport across basolateral membrane
- Fructose is absorbed in a separate two step process
  - GLUT 5 transporter – transport across apical membrane
  - GLUT 2 transporter – transport across basolateral membrane
Nutrient Absorption: Co-Transport

Active transport on basal membrane maintains concentration and electrical gradient for Na⁺ across tubular endothelial cell – allows for glucose and amino acids transport by facilitated diffusion.

Fructose is transported by facilitated diffusion, not co-transported with sodium; rate of transport is ½ that of glucose.
Carbohydrate Absorption

- Principal products of digestion (glucose & galactose) are transported by specific carrier proteins & coupled to active Na\(^{+}\) transport
  - Specificity for molecules with a d-pyranose ring structure and an OH\(^{-}\) at C\(_2\) configured like glucose
  - Competitive inhibition between sugars that meet specificity reqmts.
  - Inhibition by phlorizin (glucoside with high affinity, but not transported)
  - Inhibition by metabolic poisons or hypoxia
  - Dependence on simultaneous Na\(^{+}\) transport
  - Inhibition by ouabain which blocks the Na\(^{+}\) pump
Protein Digestion

Proteins $\xrightarrow{\text{pepsin}}$ Proteoses Peptones Polypeptides

Polypeptides $+\ Amino\ acids$ $\xrightarrow{\text{peptidases}}$ Amino acids

Amino acids are rapidly absorbed into portal blood
Protein Digestion

- Absorption: similar to carbohydrates
- Enzymes used: pepsin in the stomach
- Enzymes acting in the small intestine
  - Pancreatic enzymes – trypsin, chymotrypsin, and carboxypeptidase
  - Brush border enzymes – aminopeptidases, carboxypeptidases, and dipeptidases
Protein Absorption

• Characteristics of Amino Acid Transport
  – Specificity of L-amino acids
  – Coupling to Na\(^+\) transport – metabolic inhibitors & ouabain
  – Competitive inhibition between amino acids using same carrier
  – Separate carriers for
    • Neutral amino acids, ie leucine, alanine, glycine
    • Basic amino acids, ie lysine, arginine
    • Proline and hydroxyproline
Protein Absorption Pathways

1. Enzymes from stomach & pancreas hydrolyze proteins to peptides, then to amino acids
2. Enzymes digest proteins to peptides; enzymes at brush border digest the peptides to amino acids
3. Enzymes digest proteins to peptides which are taken up as oligopeptides and hydrolyzed to amino acids in cytoplasm
4. Enzymes digest protein to oligopeptides which are taken up and moved directly into blood
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Protein Absorption Pathways

Intestinal lumen
Proteins
- Trypsin
- Chymotrypsin
- Carboxypeptidases A and B
- Elastase

Oligopeptides

3 - 8 + residue oligopeptides

Di- and Tripeptides

Amino acids

Penultimate proline or alanine

Membrane
Brush border

Amino-oligopeptidase
Amino acid transport proteins
Amino peptidases

Di- and Tripeptides

Peptide transport protein

Dipeptidyl aminopeptidase

Cytosol

Amino acids

Cytoplasmic peptidases
- Prolidase
- Dipeptidase
- Tripeptidase

Amino acids
Absorption of Oligopeptides

Peptides enter cell via H⁺/oligopeptide co-transporter. Peptidases hydrolyze peptide into constituent amino acids which are transported out of cell by one of three amino acid transporters.
Lipid Digestion

Fat digestion

Fat $\xrightarrow{(Bile + Agitation)}$ Emulsified fat

Emulsified fat $\xrightarrow{Pancreatic lipase}$ Fatty acids and 2-monoglycerides

Fat hydrolysis

$\text{CH}_3-(\text{CH}_2)_{16}-\text{C}=\text{O}-\text{CH}_2$

$\text{CH}_3-(\text{CH}_2)_{16}-\text{C}=\text{O}-\text{CH} + 2\text{H}_2\text{O}$ $\xrightarrow{\text{Lipase}}$

$\text{CH}_3-(\text{CH}_2)_{16}-\text{C}=\text{O}-\text{CH}_2$

(Tristearin)

$\text{CH}_3-(\text{CH}_2)_{16}-\text{C}=\text{O}-\text{CH} + 2\text{CH}_3-(\text{CH}_2)_{16}-\text{C}=\text{OH}$

(2-Monoglyceride) (Stearic acid)
Lipid Digestion

• Absorption: Diffusion of fatty acids into intestinal cells where they:
  – Combine with proteins and extrude as chylomicrons
  – Enter lacteals and are transported to systemic circulation via lymph

• Glycerol and short/medium chain fatty acids (<10-12 carbons) are:
  – Absorbed into the capillary blood in villi
  – Transported via the hepatic portal vein

• Enzymes/chemicals used: bile salts and pancreatic lipase
Lipid Digestion

- For a molecule to be soluble in water, it must have accessible polar groups
- Hydrocarbon chains are non-polar; insolubility increases in proportion to chain length
- The object of lipid solubilization is to incorporate the dietary lipids into micelles from bile
- Types of lipid digestion
  - Hydrolysis followed by micellar dispersion (long-chain triglycerides)
  - Micellar dispersion alone without lipolysis (fat soluble vitamins A,D,E,K & cholesterol)
  - Hydrolysis alone (micellar dispersion unnecessary since hydrolytic products are water soluble, ie medium chain triglycerides, 8-12C)
Fat Emulsification

Large lipid droplet is divided into smaller droplets in lower portion of stomach and the small intestine – mechanical disruption – and prevented from reforming by emulsification – nonpolar portions of phospholipids and bile salts combine with nonpolar lipid droplets, leaving polar end exposed to water surface and lipase action.
Fat Digestion

The products of fat digestion by lipase are held in solution as micelles – consisting of bile salts, fatty acids, monoglycerides, and phospholipids.

Hydrolysis of triglyceride is necessary before micelle solubilization can occur – role of lipase.
Fat Absorption

Free fatty acids and monoglycerides enter epithelial cell by diffusion

In the epithelial cell, ffa and monoglycerides are resynthesized into triglycerides – lowering concentration of monoglycerides and ffa, maintaining diffusion gradient

Triglycerides are formed into chylomicrons – lipid rich particles containing TG, phospholipids, cholesterol, fat-soluble vitamins – which pass into lacteals (lymphatic capillaries) and enter into circulation via thoracic duct
Formation of Chylomicrons

1. Long-chain fatty acids and other products of lipid digestion are converted back to triglycerides, phospholipids and esters of cholesterol in the SER.

2. Fat droplets form in the cisternae of the SER.

3. Apoproteins are synthesized in the RER and then transferred to the SER, where the apoproteins associate with lipid droplets.

4. Nascent chylomicrons and VLDLs arrive at the cis face of the Golgi apparatus. Here, apoproteins are glycosylated.

5. Vesicles carrying chylomicrons or VLDLs bud off from the trans-Golgi apparatus, and move to the basolateral membrane in transport vesicles.

6. Transport vesicles fuse with the basolateral membrane, releasing chylomicrons or VLDLs.

7. Chylomicrons and VLDLs pass through large interendothelial channels of lymphatic capillaries, and enter the lymph.

8. Glycerol, short-chain, and medium-chain fatty acids pass through the enterocyte and enter blood capillary.
Electrolyte Absorption

• Most ions are actively absorbed along the length of small intestine
  – Na\(^+\) is coupled with absorption of glucose and amino acids
  – Ionic iron is transported into mucosal cells where it binds to ferritin
• Anions passively follow the electrical potential established by Na\(^+\)
• K\(^+\) diffuses across the intestinal mucosa in response to osmotic gradients
• Ca\(^{2+}\) absorption:
  – Is related to blood levels of ionic calcium
  – Is regulated by vitamin D and parathyroid hormone (PTH)
Water Absorption

- 95% of water is absorbed in the small intestines by osmosis
- Water moves in both directions across intestinal mucosa
- Net osmosis occurs whenever a concentration gradient is established by active transport of solutes into the mucosal cells
- Water uptake is coupled with solute uptake, and as water moves into mucosal cells, substances follow along their concentration gradients