Gastrointestinal Motility 1: Oral, Esophageal, and Gastric Motility
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OBJECTIVES:

1. Contrast the two types of electrical activity of the gut.
2. Explain the interaction of the muscle layers.
3. Describe the neural and muscular events that mediate swallowing.
4. Compare the electrical activity in different regions of the stomach and describe how they lead to different physiological role of each region.
5. Describe the gastric motor activity during filling, digestion and emptying.
6. Explain the role of the duodenum in regulating gastric function.

Suggested Reading: Berne & Levy pp.543-563

1. CHARACTERISTICS AND REGULATION OF GUT SMOOTH MUSCLE

A. General Characteristics

1. Smooth muscle cells are coupled to each other by means of gap junctions between cells. This allows electrical events to spread rapidly from cell to cell. These gap junctions also allow second messengers (e.g. IP3/cAMP) and ions (e.g. Ca^{2+}) to spread from cell to cell.
2. Because of this coupling, the contractile unit is not a single muscle cell but rather it is a sheet of muscle. This sheet that acts as a single contractile unit is called a functional synctium. This type of smooth muscle is know as Unitary type of Smooth Muscle.
3. Resting membrane potential is not stable but rather shows spontaneous oscillations (slow waves). Also absolute level and rate of depolarization varies in different areas of the gut.
4. Two types of electrical activity can be identified.
   a. Slow waves (also called basic electrical rhythm or control potentials)
   b. Spikes or muscle action potentials.

B. Electrical Activity

1. SLOW WAVES: (Figures 1 & 2) Membrane potential is not stable but rather shows slow cycles of depolarization and repolarization.
These cycles differ in speed, amplitude, frequency, and duration in different regions of the gut. The wave consists of a rapid upstroke (depolarization), a partial repolarization, a sustained plateau lasting several seconds, and a complete repolarization to resting level. The slow wave spreads electrically in the longitudinal and circular directions as well as through the thickness of the muscle. All gut muscle cells appear to be capable of generating slow waves however, usually cells are coupled via gap junctions to pacemaker cells called Interstitial Cells of Cajal (ICC). These are specialized cells whose membrane potential oscillates at a higher frequency than the intrinsic frequency of smooth muscle cells. There are many subtypes of ICC that perform other actions such as acting as intermediates between nerves and muscle. Pacemaker ICC are located at the myenteric level where circular and longitudinal muscle intersect and at submucosal level where circular muscle and submucosa intersect. Intramuscular ICC are located throughout the thickness of the circular muscle and have gap junction contacts with muscle cells and neurons.

Figure 1.
a. Slow waves are the result of influx of Ca\(^{2+}\), and possibly other ions, causing initial depolarization. The Ca\(^{2+}\) current slowly inactivates and is balanced by an outward potassium current. Eventually the potassium current dominates leading to repolarization.

b. The amplitude and duration of plateau phase are determined by the magnitude of the Ca\(^{2+}\) influx. Hormones and transmitters can modify the plateau. Excitatory agents (e.g. acetylcholine, substance P, CCK) increase the duration and amplitude, of the plateau potential. If the **plateau potential** exceeds the threshold level for voltage-activated calcium channel opening, then more Ca\(^{2+}\) enters and contraction occurs (Figure 3); inhibitory agents (e.g. vasoactive intestinal peptide) lower amplitude and duration of the plateau phase thereby decreasing the likelihood of contraction.
2. **SPIKES (Action Potentials):** These occur when membrane potential is above threshold for opening voltage-dependent Ca\(^{2+}\) channels on smooth muscle membrane and is usually seen in intestinal muscle. Opening of these channels results in rapid and complete depolarization of the cell. The rise in intracellular Ca\(^{2+}\) is rapid but voltage sensitive Ca\(^{2+}\) channels rapidly inactivate as K channels open. Inactivation of inward calcium currents and activation of outward potassium currents lead to reversal of membrane potential (repolarization). The spike potential are always accompanied by but are not necessary for contraction. The amplitude of contraction is determined by the number of spikes superimposed on the slow waves. (Figure 4)
A. Innervation of muscle layers

1. The thinner longitudinal smooth muscle contains few nerve fibers. This muscle is contracted primarily by acetylcholine which diffuses into the longitudinal muscle layer after being released from neurons at the junction of the myenteric plexus and the longitudinal muscle. This layer also contains a very sparse innervation by inhibitory nerve fibers so that relaxation is mainly due to inhibition of the release of the excitatory transmitter, acetylcholine.

2. The thicker circular muscle layer contains many neurons of a variety of types. The neurons do not make true synapses with muscle cells but rather release transmitter from varicosities along the length of the axon. The excitation or inhibition then spreads throughout the sheet of muscle via gap junctions. The predominate innervation is by relaxant (VIP and nitric oxide synthase-containing) nerves.

3. There is recent evidence that in some regions and species, the interstitial cells of Cajal are also innervated by neurons of the myenteric plexus. In this manner the contractile activity of the muscle and electrical potential of the cell can be coordinated.

B. Coupling between muscle layers

1. In general, the circular and longitudinal muscle contractions are out of phase. That is, the circular muscle layer is inhibited (relaxes) when the longitudinal muscle layer contracts and visa versa. This prevents the two layers from contracting at the same time and is the result of reciprocal innervation of the two layers by inhibitory neurons of the myenteric plexus.

2. Contraction of the longitudinal layer coincident with relaxation of the circular muscle shortens and widens the gut. This has the effect of creating a segment that is relaxed and easy to push material into. In contrast, contraction of the circular layer and relaxation of the longitudinal layer decreases the radius and lengthens the gut. This results in an increase in the intra luminal pressure which is the driving force to move material through the gut.

3. These two events occur in a coordinated manner as controlled by the enteric nervous system.

4. Stimulation of the gut by chemical components of chyme, mechanical movement of mucosa, or by distension results in contraction of the circular muscle and relaxation of longitudinal muscle above (orad) the site of distension. This increases intraluminal pressure and tends to push the material anally. At the same time, the circular muscle below (caudad) the site relaxes and the longitudinal layer contracts providing a relaxed region into which the material can be easily propelled. The contraction of longitudinal muscle pulls the gut up and over the material also aiding in the anal propulsion. (Figure 5). The coordinated
response orad and caudad to a site of stimulation is known as the Law of the Intestine. This basic law defines movement throughout the gut, and is an example of a Short Arc Reflex called the Peristaltic reflex.

5. Contraction of circular muscle above the site of distension is mediated by cholinergic neurons and tachykinin containing (substance P) neurons. Relaxation below the site of distension is mediated by VIP/Nitric oxide synthase-containing neurons.

C. Patterns of motility (based on above law and wholly mediated through neuronal circuits of myenteric plexus)

1. **Tonic or sustained contraction**: this type of contraction is seen in sphincters, proximal stomach, and gallbladder. Muscle in one area remains contracted over time. Neural innervation is usually inhibitory and serves to relax the muscle.

2. **Segmental contraction**: mixing contractions in local area which are not propagated (Figure 6). Common in small intestine and colon.

3. **Peristaltic contractions**: propulsive, propagated contractions which move luminal contents towards the anus (Figure 6). Basically, this is a moving ring of contraction preceded by a moving ring of relaxation. This is found throughout the gut (except proximal stomach) in regions concerned with movement of chyme.
III. SWALLOWING AND ESOPHAGEAL MOTILITY

A. Chewing

1. Can be voluntary initially but becomes reflexive.
2. Begins to break down food mechanically and mixes food with salivary secretions.

B. Swallowing: Initial events

Swallowing is initiated voluntarily, but then proceeds reflexively. The initial stimulus is mediated by activation of sensory nerve endings in the pharynx that respond to touch. These sensory nerves then activate the swallowing center located in the lower pons and medulla of the brain stem. Once activated, the swallow begins by activation of cranial nerves followed by activation of the vagal nerve to the esophagus.

The swallow can be divided into three phases.

1. **Oral or voluntary phase**
   
a. The tongue separates a portion of the food in the mouth and isolates it by elevating against the hard palate. The tongue then pushes the bolus into the pharynx

2. **Pharyngeal phase**
   
a. Stereotyped, reflexive sequence of events.
b. Soft palate elevates to seal off nasopharynx.
c. Epiglottis closes over the larynx to close opening to trachea. (Respiration is inhibited).
d. The upper esophageal sphincter relaxes and the pharynx contracts to propel the bolus into the esophagus (following the law of the intestine).
e. The upper esophageal sphincter contracts behind the bolus (Figure 7).

Figure 7.

3. **Esophageal phase** (Figure 8)

   a. Bolus distends the wall of the esophagus which initiates a peristaltic contraction orad and relaxation caudad, as described above.
   b. Peristaltic contraction-relaxation complex which follows pharyngeal and oral phase is called *primary peristalsis*. Often residual food or a pill caught in the esophagus distends the esophagus and initiates a peristaltic contraction not preceded by the oral and pharyngeal phases. This is called *secondary peristalsis*.
   c. The afferent and efferent neurons mediating peristalsis in the esophagus are vagal fibers. The afferents project to the brain stem nucleus ambiguus and the vagal motor complex (Nucleus of the tractus solitarius and the Dorsal motor nucleus). The efferent fibers to the striated part of the esophagus directly innervate and contract the skeletal muscle via release of acetylcholine. The efferent fibers to the smooth muscle portion
innervate enteric cholinergic neurons that cause contraction and VIP/nitric oxide (NO) neurons that cause relaxation (Fig. 8)

4. Lower esophageal sphincter (LES)

a. Sphincter at junction of esophagus and stomach relaxes as bolus approaches.

b. This relaxation is mediated by the release of vasoactive intestinal peptide and nitric oxide from myenteric neurons.

c. Relaxation is followed by contraction (rebound) as bolus passes into stomach. Thus the LES follows the same stereotyped sequence described for peristalsis. (Figure 8).

IV. GASTRIC MOTILITY

A. Functional anatomy
1. The stomach may be divided into sections based on anatomy and function (Figure 9). The major functions of stomach are:
   a. act as a reservoir,
   b. grind and mix food with secretions,
   c. regulate the delivery of nutrients to small intestine.

2. The upper (Proximal) portions are the **fundus and orad corpus**. These regions are tonically contracted at rest due to a low resting membrane potential (-48mv) that allows Ca$^{2+}$ channels to remain open. They have no slow waves or myoelectrical rhythm (Figure 10). This region of the stomach is non-propulsive but rather serves as the major storage site for a meal.

3. The **corpus** (mid and caudad) serves as both storage and mixing sites. The muscle is thicker than that of the fundus and demonstrates slow waves (Figure 10). The meal is slowly mixed with gastric secretions by contractions in this area over several hours.

![Diagram of the stomach](image)

Figure 9.
4. The **antrum (distal stomach)** has a very thick circular muscle layer and demonstrates slow waves with superimposed action potentials or spikes. (Figure 10). Contractions in this area are very strong and serve to grind solid particles and to propel material into the small intestine. Often referred to as the **antral pump**. The resting membrane potential here is about -75 mv at its nadir.

5. Final area at junction of antrum and duodenum is the **pylorus or pyloric sphincter**. This is tonically contracted and its activity is often coordinated with that of the antrum.
B. Reservoir Function

1. The initial motility of the stomach can be divided into 3 phases as indicated in Figure 11. These phases are the result of motility effects in the proximal (fundus and orad corpus) portions of the stomach.

   - **Phase I:** At rest before a meal begins, the stomach is flaccid and empty because of the dominant inhibitory tone of the enteric nervous system and because there are no stimuli to induce motility.

   - **Phase II:** As a meal begins, swallowing delivers food from the oral cavity as a bolus. As the bolus approaches the Lower Esophageal Sphincter, the proximal stomach relaxes to allow the bolus to pass into the stomach and to allow the stomach to expand without a significant increase in pressure. This is called *Receptive Relaxation* (Figure 12 & 13). This is mediated by a *vago-vagal long arc reflex* initiated by vagal afferent fibers in the esophagus and vagal efferent fibers that innervate inhibitory motor neurons of the enteric nervous system. The latter release vasoactive intestinal peptide and nitric oxide causing relaxation of the proximal stomach.

   - **Phase III:** As the meal progresses, the increased delivery of material distends the wall of the stomach more, activating both vagal afferent fibers and local intrinsic primary afferent neurons. These initiate additional *vago-vagal long arc* and *short arc reflexes* that activate the same inhibitory motor neurons leading to greater relaxation of the proximal stomach. This is called *Adaptive Relaxation*. (Figure 12 & 13). This also prevents the distension of the stomach from causing an increase in pressure as evident from the rise in pressure following vagotomy (Figure 13).
Adaptative Relaxation
Receptive Relaxation

Figure 12.

Receptive Relaxation of Proximal Stomach is dependent on Vagus

Figure 13.
C. Gastric Motility

1. **Pacemaker cells (Interstitial Cells of Cajal)** located in the corpus along the greater curvature initiate slow waves at a rate of 3/min. These induced a moving **Peristaltic or Propagating Contraction** wave that moves distally towards the antro-pyloric region with increasing strength and speed.

2. Movement of luminal contents depends on four events or forces (FIGURE 14)
   a. Propagating Peristaltic contraction
   b. Gastric tone
   c. Gastric emptying
   d. Retropulsion

3. **Retropulsion** is the process of pushing larger particles back into the proximal stomach as the propagating contraction pushes liquid and smaller (few mm) particles distally.

D. Gastric Emptying (FIGURE 15)

1. This requires the coordination of actions of all parts of stomach: Corpus, antrum, and pylous as well as duodenal bulb and duodenum.

2. As the peristaltic wave pushed material distally, the **pylorus/pyloric sphincter** is closed (Phase of propulsion). The peristaltic wave enters the antral region where it becomes forceful and rapid. The contraction crushes large particles and sends some liquid and small particles through the pylous, which is beginning to open. As the peristaltic wave reaches the pylous, it opens wide allowing chyme to flow into the duodenum (Phase of Emptying). About 10 ml passes with each peristaltic wave. The pylorus then closes (as does the duodenum) preventing the movement of chyme into the duodenum. At this point,
the antropyloric contraction further crushes material and propels material back into the corpus (Phase of retropropulsion).

3. The process also acts as a sieve to insure that only small particles enter the small intestine.

![Figure 15](image)

4. There is a difference in the rate of gastric emptying of liquids and solids (Figure 16). Since liquids empty without the need to be reduced in size by antral grinding, an isosmotic non-nutrient fluid meal begins to empty immediately. The rate of emptying is proportional to the square root of the volume remaining in the stomach. The rate of emptying of a solid, isosmotic, non-nutrient meal, demonstrates a delay or lag time for grinding of solid to a size that will pass through the pylorus. Emptying then proceeds as described for liquids. Nutrient meals have additional controls as outlined below.
E. Regulation of Gastric Emptying of Chyme

1. Gastric emptying rate is influenced by both neural and hormonal mechanisms.
2. **Mechanoreceptors**, activated by distension, are present in the wall of the stomach and duodenum.
3. Distension of the stomach accelerates emptying whereas distension of the duodenum slows emptying of the stomach.
4. Distension-induced effects are most likely neurally-mediated reflexes involving both enteric neurons (short arc reflex) and vagal afferent (sensory) and efferent (motor) neurons. The latter is called a **vagovagal reflex** and is an example of a **long arc reflex**.
5. **Chemoreceptors** in mucosa of upper small intestine (esp. duodenum) are sensitive to components of the chyme and activate neural reflexes which slow gastric emptying.
6. Components of chyme can also slow gastric emptying as a result of the release of gut hormones from mucosal (and pancreatic) enteroendocrine cells.

F. Components of Chyme which Slow Gastric Emptying

1. **Acid** (esp. HCl)-release of secretin.
2. **Lipid digestion products** (e.g. fatty acids)-release of cholecystokinin and GIP (and possibly Pancreatic Polypeptide (PP) from pancreatic islets).
3. **Protein digestion products** (e.g. amino acids) -release of CCK and gastrin.
4. **Osmolarity**—both hypo- and hyperosmolar solutions slow gastric emptying. Digestion of starch (i.e., carbohydrate) cause rapid rise in osmolarity of chyme in duodenum.

5. Lipid digestion products are most effective at slowing gastric emptying. This may be related to higher caloric content of fat vs protein and carbohydrate. High caloric meals empty slower than low caloric meals.

6. Recent evidence suggests a novel cite of action of CCK on sensory mechanoreceptors in wall of stomach. CCK activates a **vagovagal reflex** resulting in release of VIP from enteric neurons in the gastric fundus. VIP causes relaxation of fundus (contractile cholinergic neurons inhibited at same time) which leads to a reduction in gastric emptying.

G. **Mechanisms of Slowing of Gastric Emptying.**

1. The slowing of gastric emptying by components of chyme is mediate by changes in gastric tone (decreased tone), antral contraction (decrease), pyloric opening time (decreased) and duodenal activity (decreased peristalsis and increased non-propulsive contractions). (Figure 17)

<table>
<thead>
<tr>
<th>Non-caloric meal</th>
<th>Feedback</th>
<th>Nutrient meal</th>
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<tbody>
<tr>
<td><strong>Antrum</strong></td>
<td>Reduced force of antral contractions</td>
<td></td>
</tr>
<tr>
<td><strong>Pylorus</strong></td>
<td>Reduced pyloric opening</td>
<td></td>
</tr>
<tr>
<td><strong>Duodenal bulb</strong></td>
<td>Reduced peristalsis</td>
<td></td>
</tr>
<tr>
<td><strong>Middle Duodenum</strong></td>
<td>Enhanced segmental activity</td>
<td></td>
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Figure 17.
V. STUDY QUESTIONS

1. Electrical slow waves
   A. Occur at the same frequency throughout the gut.
   B. Cause an increase in the influx of sodium ions.
   C. Normally originate in the Interstitial Cell of Cajal.
   D. Are present in unitary and multi-unit smooth muscle.
   E. Cause the release of second messengers within muscle cells.

2. Vasoactive intestinal peptide
   A. Is a hormone that causes muscle contraction.
   B. Causes contraction of sphincteric muscle.
   C. Mediates relaxation caudad (anal) to a distension.
   D. Is structurally related to gastrin and cholecystokinin.
   E. Increases the number of spikes on intestinal slow waves.

3. Secondary peristalsis of the esophagus
   A. Is a hormonally mediated wave of contraction.
   B. Is a peristaltic wave that moves from lower to upper esophageal sphincter.
   C. Begins in the pharynx instead of the oral cavity.
   D. Does not require relaxation of the lower esophageal sphincter.
   E. Occurs independent of primary esophageal peristalsis.

4. The gastric slow wave with the longest duration occurs in the
   A. Fundus.
   B. Orad Corpus.
   C. Middle Corpus.
   D. Orad antrum
   E. Caudad antrum

Answers: 1=C, 2=C, 3=E, 4=E