SMOOTH MUSCLE
Smooth muscle lines the walls of hollow organs (e.g., intestine, uterus), the circulatory system (arteries and veins), and ducts of secretory glands. The primary role of smooth muscle is to regulate the diameter of the organ lumen which it surrounds. Although "smooth muscle" is used to categorize muscle components of these various tissues, there is a large degree of heterogeneity with respect to specific physiological responses and pharmacological sensitivities. On the other hand, smooth muscle is characterized by a slow speed of contraction, and an ability to maintain tension for long periods at low energy cost. These functional properties of smooth muscle suit its physiological responsibilities: maintenance of "organ" volume for extended periods (arteries) and slow rhythmic propulsion (intestine, uterus). Most smooth muscles exhibit strong electrical coupling through gap junctions, and only few areas of innervation. Smooth muscle of the cardiovascular system rarely show spontaneous electrical activity, and are primarily activated by agonist gated mechanisms, whereas "visceral" smooth muscles of the gut and uterus demonstrate spontaneous spike discharges which provide regulated propulsive contractions.

ALIMENTARY TRACT MOTILITY

1. What is the role of the LES and Proximal Stomach in the normal swallowing response?
2. What are the regulators of gastric emptying and how do they operate.
3. How does the rate of transit through the alimentary canal effect digestion and absorption?
4. What are the functional consequences of the frequency gradient for slow wave activity in the small intestine?

I. Basic Mechanisms for Alimentary Motility.

Patterns of alimentary canal motility can be delineated into two distinct periods: Digestive and Inter-digestive. The inter-digestive period is when no digestion products (referred to as chyme) are resident proximal to the large intestine. This period normally exists during sleep, and is ended when cephalic signals initiate a completely different pattern of motility that is associated with the digestive and absorptive functions of the canal.

A distinct pattern of alimentary functions are observed during the digestive period which begins when signals such as sight of appetizing foods and smells initiate feeding behavior. The events of digestion involve both mechanical and chemical breakdown of ingested material. For these processes to be carried out optimally, the alimentary organs must balance two opposing functions. On one hand, contents must be held long enough for breakdown and mixing to occur. On the other, gastrointestinal contents must be moved analward (aboral) to make room for more food and to remove wastes. The neural-hormonal-muscular apparatus of the alimentary tract regulates and coordinates motility to accomplish these important aspects of digestion. The longitudinal muscle layer is used to rhythmically shorten and lengthen the canal thereby propelling the digestate (chyme) along the tract. Rhythmic contraction of the circular layer is used to mix contents, restrict movements at specific sites (sphincters), but also propel chyme more slowly than then longitudinal contractions.
A. Visceral Smooth Muscle. Smooth muscle cells lining the alimentary canal are coupled electrically by gap junctions. Therefore, they function as a syncytium with activity spreading laterally between cells. Pacemaker smooth muscle-like cells (referred to as: Interstitial Cells of Cajal) exhibit reproducible phasic changes in resting membrane potential. These waves of depolarization and repolarization propagate to the contractile smooth muscle where they are called slow waves. Although slow waves are observed continuously, for extended periods the resting membrane potential does not reach threshold for firing of action potentials (ex. inter-digestive period). Since action potentials are required to initiate Ca^{2+} influx into the smooth muscle cell, the pattern of rhythmic depolarization/repolarization cycles are observed without concomitant contractile activity. The level of depolarization does not reach threshold because enteric neurons feed inhibitory signals to the interstitial cells of Cajal limiting their level of depolarization but not influencing the frequency of the rhythm. Sensory input into the enteric interneurons determine the level of inhibition placed upon slow waves, and thereby, the contractile state of the muscle. Local distension blocks the inhibitory output allowing the smooth muscle cells to reach threshold with ensuing activation of rhythmic contractility.

Tetrodotoxin blocks Na^{+} channels required for transmission of neural inputs, but does not influence channels within the smooth muscle cells. Thus, this drug can be added to block inhibitory signals to the smooth muscle. Action potentials become apparent because the level of depolarization in the smooth muscle cell is allowed to reach threshold after TTX treatment (removal of neuronal inhibition). The action potentials lead to opening of voltage dependent Ca^{2+} channels, elevation of intracellular Ca^{2+} and smooth muscle contraction as shown by the increase in force generation. Normal stimuli which lower enteric inhibition are related to local distention of the alimentary canal, chemical sensory input, or peripheral signals all of which are integrated within the enteric nervous system.

![Relation between Cell membrane potential and contraction in intestinal smooth muscle.](image)

Figure 1. Slow wave frequency observed in cells from the jejunum. Addition of TTX blocks transmission of inhibitory signals from the enteric nerves to the smooth muscle leading to a more profound depolarization, and development of action potentials with subsequent smooth muscle cell contraction.
B. Functions of Muscle Motility. There are three primary functions that motility plays in the alimentary canal. In the stomach and colon, tonic contraction or relaxation of the circular muscle layer allows these organs to act as reservoirs for chyme. A second role is that of mixing the contents within the lumen. This is particularly important in the distal stomach where particles of food are mechanically broken down, but mixing is also critical in the intestine and colon for optimal digestion and absorption of nutrients. Finally, Propulsion is required to move chyme and feces in regular patterns. Propulsive contractions occur intermittently throughout the alimentary canal, and generally require long neuronal reflex arcs to coordinate the contractile activity.

II. Motility of Alimentary Organs

A. Esophagus: Esophageal peristalsis begins with a voluntary swallow; the progression of the contractile wave through the esophagus is involuntary. The esophageal body is "guarded" at the upper end by the upper esophageal sphincter and the gastroesophageal junction by the lower esophageal sphincter (LES). The initial 1/3 of the esophagus is lined with skeletal muscle. Initiation of a swallowing event elicits a programmed reflex providing relaxation below the bolus with subsequent contraction as the chyme moves past. The lower 2/3 of the esophagus is lined with smooth muscle. In general, the majority of a bolus is removed from the esophagus during the initial swallow. Any food remaining in the esophagus causes distension of the lumen. This distension is sensed by pressure receptors in the lumen wall which induces a local reflex to initiate secondary contractile waves limited to the smooth muscle region. The initial programmed event is referred to as Primary Peristalsis while Secondary Peristalsis refers to the distension mediated events in the smooth muscle required for full esophageal clearing.

As part of the programmed reflex of primary peristalsis, the LES and proximal stomach relax as the bolus moves down the esophagus. The LES quickly regains tone as the bolus enters the stomach which increases local pressure at the LES to block retropulsion of stomach contents. Conversely, the proximal stomach adjusts tone (relaxes) to maintain pressure constant even though food has entered. A competent LES is required not only for normal filling of the stomach, but also for protection against reflux of acid from the stomach back into the esophagus. Such reflux is the basis for "heart burn" which is caused by damage to tissue of the LES and lower esophagus. Consistent damage can lead to abnormal release of the bolus into the stomach, as well as, esophageal cancers.
B. Gastric Motility

The stomach serves as a storage organ ("proximal" stomach), and as a "grinding mill" which mechanically and chemically breaks down food ("distal" stomach). The emptying of chyme from the stomach into the small intestine also is highly regulated with the primary factors mediating the rate of emptying being both the physical and chemical composition of the meal itself.

As a bolus of food passes through the LES, tone of the smooth muscle in the proximal stomach is reduced. No change in pressure within the stomach lumen is observed even though food has entered (Figure 2). The increase in diameter to accommodate the incoming food is referred to as receptive relaxation. If the vagus nerve is cut, receptive relaxation does not occur, or is significantly limited causing stomach pressure to increase upon ingestion. The reservoir function of the proximal stomach is dependent on the ability to accommodate food without change in pressure. Therefore, after vagotomy, the resulting high pressure in the proximal stomach leads to reflux of stomach contents into the esophagus, and premature emptying into the intestine causing malnutrition and damage to the lining of the intestine and esophagus. In addition, during pregnancy the LES is often pushed up through the diaphragm, and progesterone has a relaxing effect on smooth muscle tone which also can cause “esophageal reflux” with resulting “heartburn”.

Gastric emptying. After a meal, the ingested food remains in the stomach for 1 to 3 hours: The driving force for emptying the stomach contents into the small intestine is provided by wall motion of the distal (2/3) stomach. Both Physical and Chemical properties of the chyme determine the rate of emptying. For example, liquids empty faster than solids (i.e.; fiber slows emptying) In addition, chemical characteristics such as the osmotic pressure, pH and fat content of the chyme as it reaches the duodenum feedback to inhibit emptying. The mechanism by which these factors feedback to regulate emptying is unclear. Osmotic changes likely lead to activation of stretch receptors in the wall of the duodenum. Nutrients may act by regulating output from other receptor cells. In both cases, the feedback is mediated through the enteric plexi which modulate output of neurons that innervate the smooth muscle of the pyloric sphincter.

Figure 3. Mechanical activity of the distal stomach assists digestion by grinding solids and mixing with acid to form liquid. Once liquid, the digestate moves rapidly into the duodenum. The rate of emptying is regulated by pyloric sphincter tone. Feedback from receptors of chemical and physical (distension) stimuli located in the duodenum regulate sphincter tone. As shown, the more acidic the chyme the slower it empties.
C. **Intestinal Motility**: As chyme moves from the stomach to the intestine, "digestive period" like functions are initiated and continue in the intestine for 3-5 hours. Mixing of intestinal juices with the chyme requires wall motion. Distension is the primary stimulus for increasing contractility eliciting its response through enteric nerves. A decrease in inhibitory output to the smooth muscle cells leads to generation of action potentials which initiate contractility. The underlying slow wave activity sets the frequency of the contractile response. Local reflexes assure that regions filled with nutrients are activated not only mechanically, but also have increased blood flow, secretory and absorptive activity. A series of rhythmic contractions localized to a specific region is referred to as **Rhythmic Segmentation**. What is usually observed are tonic constrictions (*segmentation*) at either end of a rhythmically contracting canal segment assuring adequate mixing of the contents therein.

![Graph showing slow wave frequency across different regions of the intestine](image)

Figure 4. The frequency of slow waves in smooth muscle is not constant along the small intestine. The rhythmic depolarization is more rapid near the pylorus and decreases continuously to the ileocecal junction.

Since slow waves set the frequency of contractions within the muscle layers, a gradient of rhythmic segmental contractions in the small intestine exists with the highest frequency in the most proximal regions. This gradient promotes aboral propulsion of the intestinal chyme because the pressure buildup is slightly greater in the proximal intestine where contractile frequency is highest. Rhythmic segmental contractions required for mixing are driven primarily by local signals (distension), and are capable of slowly moving chyme throughout the intestine. Conversely, **peristaltic contractions** are used for movement of chyme over longer distances rapidly. Peristalsis requires the release of tonic contractions (circular muscle) to open the lumen coupled to a wave of contractile activity (longitudinal muscle) initiated behind (*proximal to*) the bolus of chyme moving analward. Therefore, peristalsis requires long reflex arcs mediated through central afferents, and loss of central reflexes (vagotomy) causes loss of coordinated peristalsis. However, chyme can still be digested and moved along the intestine, and nutrients absorbed without central control due to propulsion based on the gradient of slow wave mediated rhythmic segmentation.
The ileocecal sphincter is critically important for maintaining normal function of the small intestine. As discussed later, large numbers of bacteria in the colon are capable of digesting nutrients and in the process producing acids. A competent ileocecal sphincter allows the digestate to move into the colon but quickly closes to retard movement from the colon. Bacterial infiltration into the ileum alters absorption of many compounds, but most importantly bile acids and vitamins leading to some profound deficiencies.

D. Inter-digestive Motility: The interdigestive period can be delineated into three distinct phases which migrate temporally along the alimentary canal. Periods of quiescence predominate (Phase I), followed by a phase of intermittent and irregular activity (Phase II). A relatively short period (5-10 min) of intense activity is then observed (Phase III) prior to resumption of quiescence. Peak levels of the hormone motilin approximately coincide with initiation of the period of intense activity in the upper duodenum. When viewed at different regions of the canal, this pattern of activity is seen to migrate aborally which effects a sweeping of the canal. The migration of contractile activity, during the interdigestive period, from the distal stomach to the distal intestine is referred to as the Migrating Motor Complex.