

Chapter 3

Gastrointestinal Motility

Early in life, children notice that strange gurgling sounds sporadically emanate from their "stomachs," particularly in periods between meals. This simple observation reflects the fact that the digestive tube is quite muscular and that muscle contractions and motility are integral parts of digestive function. It follows that derangements in gastrointestinal motility can cause or result from digestive tract disease and that drugs which alter gastrointestinal motility affect digestive function.

Two fundamental patterns of motility are conducted by the digestive tube:

Propulsion: foodstuffs must be propelled along the length of the digestive tube in order to be subjected to the sequential series of processing involved in disassembly and absorption.

The principal type of propulsive motility, seen particularly in the esophagus and small intestine, is **peristalsis** - a ring of muscle contraction appears on the oral side of a bolus of ingesta and moves toward the anus, propelling the contents of the lumen in that direction; as the ring moves, the muscle on the other side of the distended area relaxes, facilitating smooth passage of the bolus.

Mixing: If ingested materials were simply propelled through the digestive tube, you would expect very poor digestion and absorption, because the digestive enzymes would not be adequately mixed with the ingesta and the bulk of the ingesta would not come in contact with the epithelial cells that absorb nutrients.

Segmentation contractions are a common type of mixing motility seen especially in the small intestine - segmental rings of contraction chop and mix the ingesta. Alternating contraction and relaxation of the longitudinal muscle in the wall of the gut also provides effective mixing of its contents.

Except for the first section of the esophagus, all the the muscle in the wall of the digestive tube is smooth muscle. Indeed, the patterns of motility seen in the gut are characteristic of smooth muscle, which has properties distinctly different from skeletal muscle.

Smooth muscle fibers are arranged in intertwined, rather indistinct bundles, aligned in most areas of the tube in circular and longitudinal layers. Individual smooth muscle fibers are connected to neighboring smooth muscle cells by gap junctions, which allow these cells to be electrically coupled. The important consequence of this electrical coupling is that when an area of smooth muscle becomes depolarized, that depolarization spreads outward through adjacent sections of smooth muscle - this results in a well-coordinated contraction of, for example, an entire ring of circular smooth muscle. Without electrical coupling through gap junctions, one would imagine that you would see contraction only of patches of circular or longitudinal muscle, which would have little effect on propulsion or mixing of ingesta.

Electrophysiology of Gastrointestinal Smooth Muscle

Normal gastrointestinal motility results from coordinated contractions of smooth muscle, which in turn derive from two basic patterns of electrical activity across the membranes of smooth muscle cells - **slow waves** and **spike potentials**.

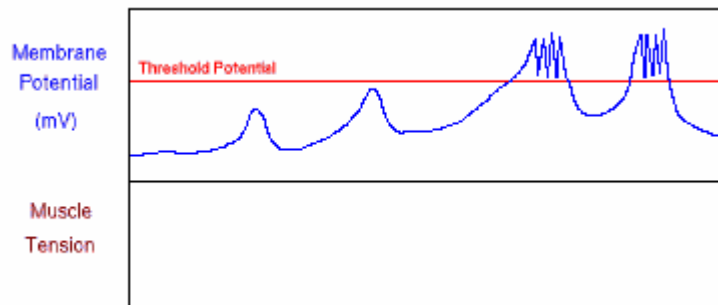
Like other excitable cells, gastrointestinal smooth muscle cells maintain a electrical potential difference across their membranes. The resting membrane potential of smooth muscle cells is between -50 and -60 mV. *In contrast to nerves and other types of muscle cells, the membrane potential of smooth muscle cells fluctuates spontaneously.*

Because the cells are electrically coupled, these fluctuations in membrane potential spread to adjacent sections of muscle, resulting in what are called "slow waves" - waves of partial depolarization in smooth muscle that sweep along the digestive tube for long distances. These partial depolarizations are equivalent to fluctuations in membrane potential of 5 to 15 mV.

The frequency of slow waves depends on the section of the digestive tube - in the small intestine, they occur 10 to 20 times per minute and in the stomach and large intestine 3 to 8 times per minute. Slow wave activity appears to be a property intrinsic to smooth muscle and not dependent on nervous stimuli.

Importantly, slow waves are not action potentials and by themselves do not elicit contractions. Rather, they coordinate or synchronize muscle contractions in the gut by controlling the appearance of a second type of depolarization event - "spike potentials" - which occur only at the crests of slow waves.

Spike potentials are true action potentials that elicit muscle contraction. They result when a slow wave passes over an area of smooth muscle that has been primed by exposure to neurotransmitters released in their vicinity by neurons of the enteric nervous system. The neurotransmitters are released in response to a variety of local stimuli, including distension of the wall of the digestive tube and serve to "sensitize" the muscle by making its resting membrane potential more positive.



Click on the graph to show (or hide) the muscle tension trace

One can now step back and understand how a particular pattern of motility is achieved. Think for a moment about what happens when a large bolus of ingested food enters the small intestine:

- The bolus distends the gut, stretching its walls.
- Stretching stimulates nerves in the wall of the gut to release neurotransmitters into smooth muscle at the site of distension - the membrane potential of that section of muscle becomes "more depolarized."
- When a slow wave passes over this area of sensitized smooth muscle, spike potentials form and contraction results.
- The contraction moves around and along the gut in the coordinated manner because the muscle cells are electrically coupled through gap junctions.

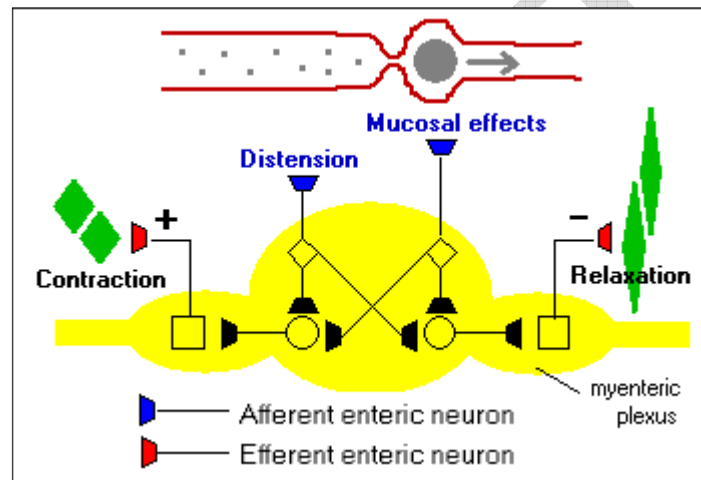
Physiology of Peristalsis

Peristalsis is a distinctive pattern of smooth muscle contractions that propels foodstuffs distally through the esophagus and intestines. It was first described by Bayliss and Starling (J Physio (Lond) 24:99-143, 1899) as

a type of motility in which there is contraction above and relaxation below a segment being stimulated. Peristalsis is not affected to any degree by vagotomy or sympathetomy, indicating its mediation by the intestine's local, intrinsic nervous system.

Peristalsis is a manifestation of two major reflexes within the enteric nervous system that are stimulated by a bolus of foodstuff in the lumen. Mechanical distension and perhaps mucosal irritation stimulate afferent enteric neurons. These sensory neurons synapse with two sets of cholinergic interneurons, which lead to two distinct effects:

- One group of interneurons activates excitatory motor neurons above the bolus - these neurons, which contain acetylcholine and substance P, stimulate *contraction of smooth muscle above the bolus*.
- Another group of interneurons activates inhibitory motor neurons that stimulate *relaxation of smooth muscle below the bolus*. These inhibitor neurons appear to use nitric oxide, vasoactive intestinal peptide and ATP as neurotransmitters.



Pregastric Digestion: Introduction and Index

An animal's or person's state of health is only as good as its nutritional state, and nutrient intake depends on normal pregastric function. Maintaining an adequate intake of nutrients is often hampered by diseases affecting pregastric function, and a solid understanding of pregastric function is necessary not only to correct diseases affecting those systems, but also to insure nutritional support in the face of all diseases.

As important as inadequate food intake is, the most prevalent nutritional disease of humans and pets in developed countries is obesity, and remarkable progress has been made in recent years to explain some of the long-standing mysteries about how we control how much we eat.

Control of Food Intake and Body Weight

The body is in a continual state of hunger, which is intermittently relieved by eating. This perpetual drive to eat is periodically suppressed by inhibitory impulses generated by such things as the presence of food in the gastrointestinal tract, the flow of nutrients into blood and other factors. After these "satiety factors" have dissipated, the desire to eat returns.

Why is it important to understand the factors that control food intake? At least two major areas of import come to mind:

- *Obesity is the most prevalent nutritional disease* of humans, dogs and cats in affluent societies such as ours, exceeding by far the number of nutritional deficiency diseases.
- *Metabolic demands of people and animals increase with sickness or trauma*, often in conjunction with anorexia. Sickness combined with anorexia leads to accelerated starvation.

Before going on, take a minute to reflect on observations you have already made about food intake, body weight and similar topics. You may have noticed, for instance, that:

- Most animals as adults maintain a remarkably constant body weight.
- When it's cold, animals and people eat more than when it's hot.
- Children maintain energy balance with wildly varying intakes of food per meal.

These kinds of observations suggest a very complex system in charge of regulating energy balance and body weight. What is known about control of food intake is often discussed in terms of short-term and long-term controls. This discussion will focus on the following areas:

- Role of the central nervous system
- Pregastric factors
- Gastrointestinal and postabsorptive factors
- Long-term controls

Role of the Central Nervous System

For many years, the hypothalamus was thought to be the key to control of food intake. This view derived from classic experiments in which food intake was studied in rats with lesions in various areas of the brain. Such studies clearly **identified two regions in the hypothalamus that dramatically influence feeding behavior**:

Gastrointestinal and Postabsorptive Factors

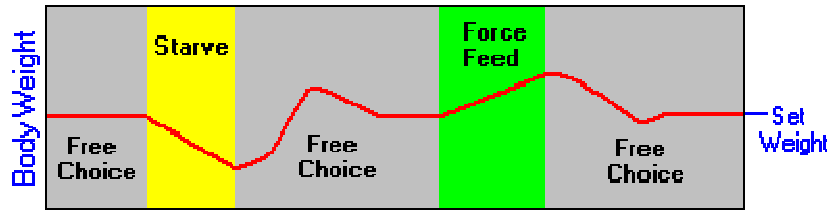
The degree of *gastrointestinal fill* is the most important signal from the digestive tract per se - a full stomach and intestine induce satiety, probably via the vagus nerve relaying that fact back to the hypothalamus. Additionally, the enteric hormone cholecystikinin is well documented to induce satiety in experimental settings, while the hormone ghrelin seems to be a potent stimulator of appetite.

As nutrients such as glucose and amino acids are absorbed, their concentrations in blood rise, as do the concentration of several hormones (cholecystikinin as mentioned above, but also insulin and glucagon). These changes also have been linked to the sensation of hunger or satiety.

Long-term Control of Food Intake

Adult animals tend to maintain a relatively constant weight known as their "*set weight*". Much of this appears to be regulated on a time scale of weeks or longer.

If an animal is starved for a long period of time, then allowed access to food, it eats a far greater amount of food than a normal animal. Conversely, if an animal is force fed for several weeks, then allowed access to free choice food, it will not eat very much. In both cases, when weight returns to "set weight," feeding behavior normalizes.



An additional interesting observation is that when food is restricted, basal metabolic rate decreases, which is one reason that it is so difficult to lose weight by dieting.

It is clear that long term regulation of body weight results from a complex integration of a battery of hormonal, metabolic and neural signals. In view of how tightly body weight is regulated in the face of widely varying levels of food intake and energy expenditure, it is clear that robust feedback systems are in place.

Searching for the feedback signals - "satiety factors" - has been a holy quest in this field for many years and has recently borne fruit, thanks to studies conducted years ago on mice with genetic mutations that cause obesity.

The satiety factor studied most extensively to date is the hormone leptin, which has the following basic characteristics:

- Leptin is synthesized and secreted predominantly by fat cells (adipocytes).
- A major site of leptin receptors is in the hypothalamus, which is known to play an important role in control of food intake and metabolic rate.
- Plasma levels of leptin rise and fall in parallel with body fat content - as body fat mass increases, so does the concentration of leptin in blood.
- Injection of leptin into leptin-deficient animals leads to reduction in body weight by suppressing food intake and increasing metabolic rate and energy expenditure.

Several other genes have been isolated that encode proteins that affect food intake, energy metabolism and body weight. Right now it is difficult to predict their future role in the pharmaceutical control of obesity, but needless to say, a number of companies are betting multimillions that one of more of these proteins will become the miracle drug for treatment of obesity.