Received: 10 August 2018 | Revised: 29 November 2018 | Accepted: 16 December 2018

DOI: 10.1111/nmo.13546

REVIEW ARTICLE

WILEY Neurogastroenterology & Motility NGM

Advances in the physiology of gastric emptying

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Funding information
This study was supported by (a) Merit Award from the VA Medical Research Service, Department of Veterans Affairs, Washington, DC (RKG); and (b) William S Middleton Award from the Department of Veterans Affairs, Office of Research and Development, Biomedical Research Laboratory, and Development Service (RKG).

Abstract

There have been many recent advances in the understanding of various aspects of the physiology of gastric motility and gastric emptying. Earlier studies had discovered the remarkable ability of the stomach to regulate the timing and rate of emptying of ingested food constituents and the underlying motor activity. Recent studies have shown that two parallel neural circuits, the gastric inhibitory vagal motor circuit (GIVMC) and the gastric excitatory vagal motor circuit (GEVMC), mediate gastric inhibition and excitation and therefore the rate of gastric emptying. The GIVMC includes preganglionic cholinergic neurons in the DMV and the postganglionic inhibitory neurons in the myenteric plexus that act by releasing nitric oxide, ATP, and peptide VIP. The GEVMC includes distinct gastric excitatory preganglionic cholinergic neurons in the DMV and postganglionic excitatory cholinergic neurons in the myenteric plexus. Smooth muscle is the final target of these circuits. The role of the intramuscular interstitial cells of Cajal in neuromuscular transmission remains debatable. The two motor circuits are differentially regulated by different sets of neurons in the NTS and vagal afferents. In the digestive period, many hormones including cholecystokinin and GLP-1 inhibit gastric emptying via the GIVMC, and in the interdigestive period, hormones ghrelin and motilin hasten gastric emptying by stimulating the GEVMC. The GIVMC and GEVMC are also connected to anorexigenic and orexigenic neural pathways, respectively. Identification of the control circuits of gastric emptying may provide better delineation of the pathophysiology of abnormal gastric emptying and its relationship to satiety signals and food intake.

KEYWORDS
digestive and inter-digestive periods, gastric emptying, gastric motility, intestinal hormones, neural control, satiety and food intake, the interstitial cell of Cajal, vagal circuits

1 | INTRODUCTION

The gastric emptying rate is a measure of the speed of delivery of gastric contents into the duodenum. Gastric contents to be delivered include liquids, digestible solids, and indigestible food residues. Over the years, advances in understanding the different physiological components of gastric emptying have been facilitated by the development of reliable, noninvasive techniques in humans.[1] The understanding of the biomechanics of the stomach helped to understand the relationship between gastric motility and gastric

Goyal R.K. Advances in the physiology of gastric emptying. First Wylie J Dodds and Sushil K Sarna Endowed Lecture of the American Neurogastroenterology and Motility Society, presented at 13th Postgraduate Course on Gastrointestinal Motility, and Neurogastro-enterology in Clinical Practice, July 29, 2018, Milwaukee, Wisconsin

emptying.[2,3] These advances began with the appreciation that gastric emptying is regulated by the physical and chemical nature of the food[4,5] through neuro-hormonal control mechanisms. Recent, ongoing studies have shown that inhibitory and excitatory vagal motor circuits and their regulatory neurons located in the solitary tract nucleus (nucleus tractus solitarius [NTS]) are responsible for the precise control of gastric emptying.[6] The NTS neurons have widespread connections with neurons in the other parts of the CNS. Gastric inhibitory and gastric excitatory hormones released from the intestine and pancreas also actively regulate gastric emptying. Many of these hormones are also involved in immediate satiety signals, and long-term food intake, energy metabolism, and bodyweight, thereby linking these metabolic changes to gastric emptying.

The precise regulation of the rate of gastric emptying of chyme (semifluid mass of partly digested food) into the duodenum is critical for further digestion and absorption in the small intestines. This regulation is provided by feedback from the intestines via a variety of gastrointestinal hormones. The rate of gastric emptying of carbohydrates and sugars is particularly an important determinant of postprandial glycemia. Slow gastric emptying may cause postprandial hypoglycemia, whereas fast gastric emptying may cause postprandial hyperglycemia. However, fast gastric emptying also upsets the release of intestinal hormones and has complex effects on glucose homeostasis. Fast gastric emptying is now recognized as a major factor in postprandial hyperglycemia and in the pathogenesis and management of diabetes mellitus (DM).[7-9]

The purpose of the present review is to synthesize the advances in the understanding of gastric motility and its neurohormonal control into an integrated model of gastric emptying.

Key Points

- There have been major recent advances in the understanding of the role neural circuits, gastrointestinal hormones, interstitial cells of Cajal and smooth muscles in the regulation of gastric emptying.
- This review presents an integrated model of the control systems in gastric emptying and its link with satiety, hunger and energy metabolism.
- This information will be valuable in understanding the relationship between gastric emptying and diabetes mellitus, developing strategies for control of hyperglycemia, pathogenesis of type 2 DM, and obesity.

2 | GASTRIC EMPTYING

The stomach performs a remarkable function of accepting large quantities of foods of different physical and chemical compositions over a short period. In humans, the stomach can expand 10-15 times its empty state volume without a significant increase in intragastric pressure (called accommodation). Water may leave the stomach promptly.[10] Digestible solids empty after they are pulverized to form chyme, which contains particles less than 2-3 mm in size.[5] Liquids and digestible solids are emptied in the digestive period that lasts 2-3 hours after a meal. However, stomach retains large food particles that escape mincing during the digestive period, and then forcefully dumps them into the small bowel during the inter-digestive period[11] (Figure 1A).

Hunt and others in the1950s and early 1960s also showed that the gastric emptying rate in the digestive period is highly dependent on volume, osmolality, the chemical composition, and caloric density of the food.[4] The average stomach empties approximately 1-4 kcal/min[12] (Figure 1B).

Because of the complex regulation of gastric emptying, proper assessment of all phases of gastric emptying requires separate studies of liquids and digestible solids of defined caloric density in the digestive period and of large indigestible particles in the

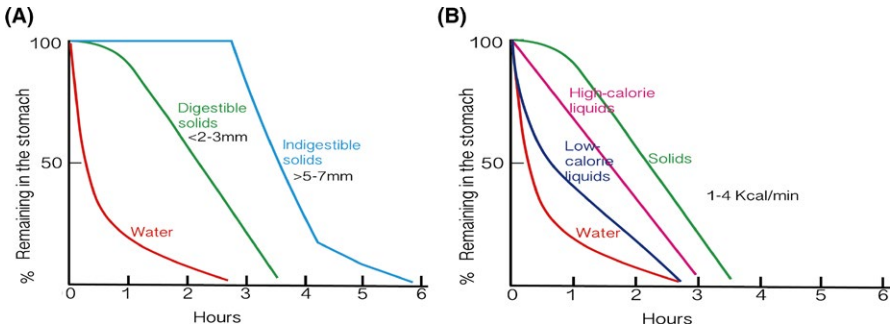

FIGURE 1 Gastric emptying rates vary with the physical characteristic and caloric density of food. (A) Effect of physical characteristics of food on the rate of gastric emptying. Note that water or 5% glucose leaves the stomach at a fast rate, and digestible solids begin to leave after a lag period and leave the stomach slowly. Large pieces of indigestible solids are retained in the stomach during the digestive period and are then rapidly emptied. (B) Effect of caloric density of the liquid meal. Note that water leaves the stomach very fast and only 50% remains in the stomach at 10 min. High-calorie liquids empty at a slower rate with 50% remaining in the stomach at 2 h. Low-calorie liquids empty at an intermediate rate so the 50% leave the stomach by 1 h

inter-digestive period. Moreover, earlier tests of gastric emptying were invasive and not repeatable. Development of noninvasive imaging and isotope techniques has now facilitated studies of gastric emptying in animals and humans.[3] Scintigraphy using technetium (99m)-sulfur colloid- or technetium (99m)-diethylenetriaminepentaacetic acid-labeled food remains the "gold standard." Time taken to empty 50% of the ingested contents (t1/2) has often been used to describe gastric emptying rate for the purposes of comparison.[13] Recently, low-fat egg white meal with measurements at 0, 1, 2, and 3 or 4 hours has been used. Gastric retention of <30 at 1 hour is indicative of fast gastric emptying, and retention of >30% at 4 hours suggests slow gastric emptying.[14] More recently, the ^{13}C breath test that indirectly measures gastric emptying has been developed. In the absence of liver or kidney disease, the results of these tests correlate well with the results of the scintigraphy. These developments have facilitated the assessment of gastric emptying in disorders of gastric emptying.[1]

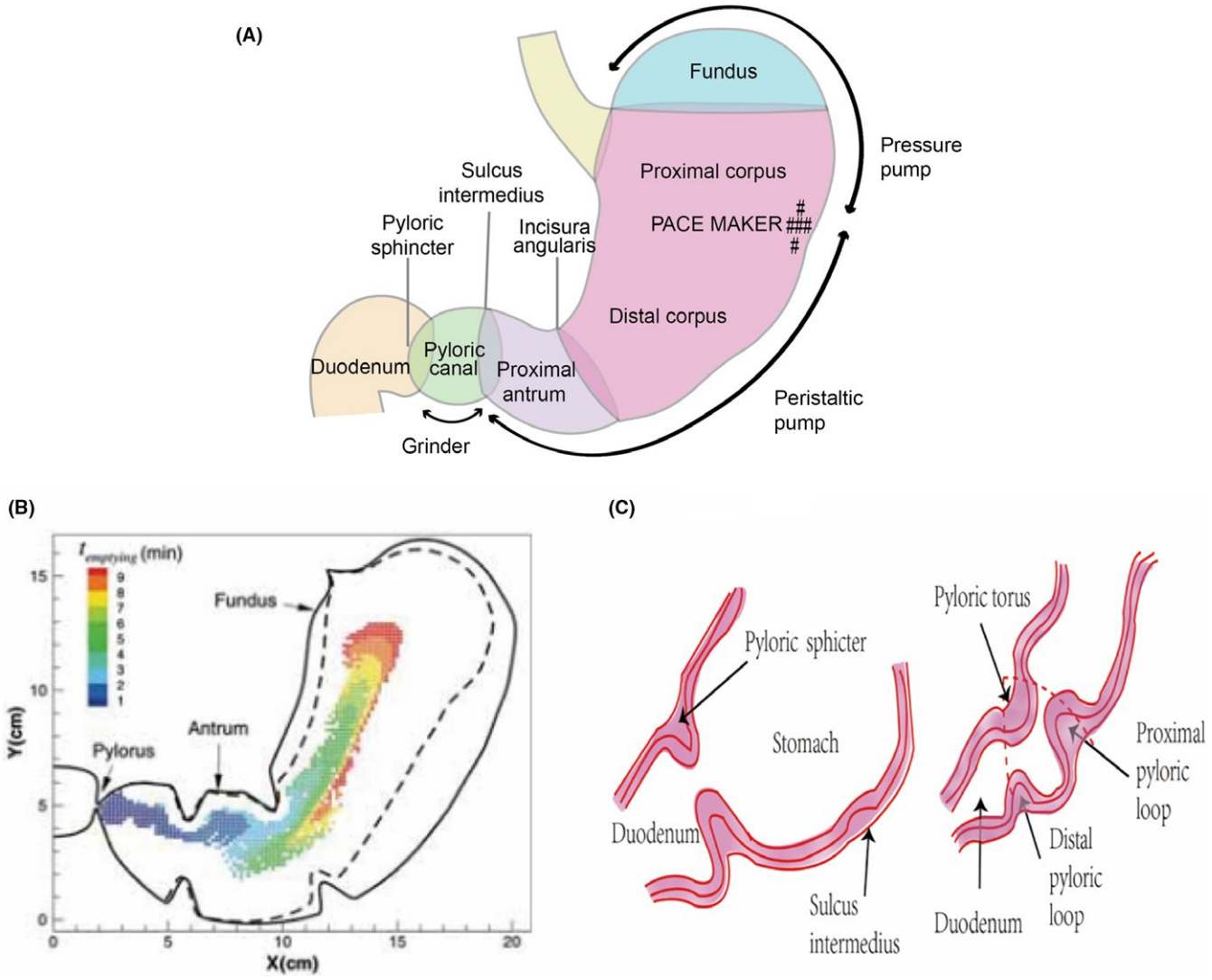

FIGURE 2 Anatomic and functional parts of the human stomach, the gastric tunnel (Magenstrasse), and the pylorus. (A) Anatomic and functional parts of the stomach. The stomach includes three multifunctional, interconnected structures: pressure pump, peristaltic pump, and a grinder. The pressure pump includes anatomic fundus and proximal corpus. The peristaltic pump includes anatomic distal corpus and pyloric antrum. The pressure and peristaltic pumps form the propulsive unit. The anatomic correlate of the grinder is the pylorus that includes the anatomic pyloric canal and pyloric sphincter. Modified from Adler.[15] (B) A functional tunnel along the lesser curvature of the stomach, called *Magenstrasse*, that may allow liquids to bypass the slower movement of the solid food through the stomach to accomplish a very fast gastric emptying. The figure identifies the initial location of particles emptied during 10 min, gray shaded with the time period of emptying, $t_{emptying}$. From Pal et al[10] (C) Details of the pyloric complex which includes the proximal muscle loop and the distal muscle loop formed by the pyloric sphincter. The proximal and distal muscle loops are ~2 cm away from each other on the greater curvature but merge together on the lesser curvature of the stomach. The loops enclose a triangular cavity with the merged muscle loops forming a torus at the lesser curve. The pyloric torus fits into the groove left between the proximal and distal muscle loops along the greater curvature, like a pastel and mortar, to form a perfect grinder. Pylorus provides mechanical grinding and food that has been tenderized by acid-pepsin, to form chyme. The proximal muscle loop and the pyloric sphincter are separately regulated and can work independently

3 | BIOMECHANICS OF GASTRIC EMPTYING

Earlier studies also defined how a single-chamber stomach can serve multiple functions such as flexible storage, grinding of food, and controlled delivery of chyme into the duodenum. In humans, the anatomic fundus and proximal corpus of the stomach serve as a flexible reservoir and a pressure pump. The distal corpus and proximal antrum constitute the peristaltic pump that primarily serves as a mixer. The terminal antrum and the pyloric sphincter form the functional grinder and filter[2,15,16] (Figure 2). The gastric emptying during the digestive and inter-digestive periods is differently regulated.

4 | GASTRIC EMPTYING DURING THE DIGESTIVE PERIOD

As the food is ingested and fills the stomach, fundic compliance increases so that a large volume of food is accommodated without an increase in pressure. In this filling phase, the pressure and peristaltic pumps remain inhibited and show no contractions. The filling phase is followed by a pumping phase, which is associated with a slow tonic contraction of the fundus and increased peristaltic contractions in the peristaltic stomach. This allows mixing of ingested food with gastric acid and pepsin and its transfer to the pylorus. The peristaltic pump also accepts food that escapes proper pulverization for recycling. The antrum fills to a certain level before food begins to enter the duodenum. This is reflected as the lag phase on the whole stomach-emptying curve.

The stomach forms a functional tunnel named "Magenstrasse," along with the lesser curvature of the stomach, that shunts liquids directly into the duodenum and bypasses the main stomach[10] (Figure 2).

The tenderized food is propelled into the pyloric grinder by contractions that become forceful in the antrum. The pylorus relaxes to receive food from the proximal antrum.[17] Pyloric contractions generate a powerful retrograde jet of food that escapes pulverization, and an anterograde jet of chyme into the duodenum. On intraluminal manometry, these events correspond with the antropyloric pressure waves (APPW) that are intimately associated with a pulsatile flow into the duodenum[18] and "sieving function".[16] Closure of the pyloric sphincter that causes complete closure of gastroduodenal communication corresponds with the isolated pyloric pressure waves (IPPW) on intraluminal manometry in humans.[19]

Enhanced or impaired relaxation of the pressure pump leads to slow or fast gastric emptying, respectively. Loss of strength or organization of contractions of the peristaltic pump leads to poor mixing and slow gastric emptying, while the increased strength of peristaltic contractions leads to the fast gastric emptying of the digestible solids[20] (Table 1).

The pyloric sphincter and the duodenum work in a well-coordinated way to regulate gastric emptying. As the pyloric complex acts as both a grinder and a variable filter, it can facilitate or inhibit gastric emptying in the digestive period. The duodenum relaxes during antral contractions—a phenomenon called "antroduodenal coordination." After accepting injections of chyme, the duodenal bulb contracts to expel the chyme in a steady flow into the second portion of the duodenum. Studies have shown that slow gastric emptying with a high-fat test meal was associated with decreased antral and increased duodenal contractile activity.[21] Moreover, duodenal contractions may cause closure of the pyloric sphincter that in turn corresponds with the isolated pyloric pressure waves (IPPW) on intraluminal manometry.[19,22]

5 | GASTRIC EMPTYING IN THE INTER-DIGESTIVE PERIOD

In the inter-digestive (fasting) period, gastric motility designed to clear the stomach of undigestible residues. It is characterized by a cyclical motor activity called the migrating motor complex (MMC).[23] The MMC is divided into four phases. Phase I lasts approximately 45-60 minutes, during which the peristaltic pump exhibits electrical slow waves that are not associated with muscle

TABLE 1 Anatomic parts, muscle type, the presence of ICC-MY, type of contraction, and effect of inhibition or excitation on different functional parts of the stomach

	Pressure pump	Peristaltic pump	Grinder
Anatomic parts	Fundus + proximal corpus	Distal corpus and proximal antrum	Terminal antrum + pyloric sphincter. Pylorus
Muscle type	Tonic	Phasic	Phasic + tonic
ICC-MY	Absent	Present	Present
Type of contractions	Tonic	Phasic, peristaltic	Strong, phasic, nearly simultaneous
Effect of increased inhibition/ decreased excitation	Slow gastric emptying	Impaired mixing Slow gastric emptying of solids	Impaired grinding Duodeno-gastric reflux
Effect of reduced inhibition/ increased excitation	Impaired accommodation and fast gastric emptying	Fast gastric emptying of solids	Outlet obstruction

TABLE 2 Neuro-hormonal activity during the digestive and inter-digestive periods

	Digestive period		Inter-digestive period			
	Immediate	Later	Phase I	Phase II	Phase III	Phase IV
Vagal activity	Increased inhibitory/ reduced excitatory	Reduced inhibitory/ increased excitatory	Increased inhibitory/ reduced excitatory	Reduced inhibitory/ increased excitatory	Non-vagal, peripheral neuro-hormonal	Increased inhibitory/ reduced excitatory
Hormonal activity	Leptin, cholecystokinin, GLP-1			Ghrelin	Motilin	
Fundus	Increasing compliance	Decreasing compliance	No pressure	Increased tonic pressure	Increased tonic pressure	Increasing compliance
Antrum	Reduced phasic contractions	Increased phasic contractions	Reduced phasic contractions	Increased phasic contractions	Migrating motor complex	Reduced phasic contractions
Pylorus	Contraction	Relaxation		Relaxation	Relaxation	Contraction

contractions. Motor quiescence is due to tonic inhibition of the motor activity. Phase II is associated with slow waves associated with frequent phasic contractions. Phase III (also called "activity front") is characterized by a front of large amplitude contractions, lasting 5-15 minutes that march toward the pyloric sphincter. The phase III of the MMC is neurally mediated and is independent of the slow waves.[24] During the migrating front, the pylorus and duodenum remain relaxed and open to allow phase III activity to sweep food residues out of the stomach.[25] Loss of pyloric relaxation leads to gastric outlet obstruction and gastric stasis.[26,27] However, enhanced relaxation of the pylorus may facilitate duodeno-gastric reflux.[27] Phase IV includes inhibition of contractile activity that merges with the next phase of digestive period activity. Vagal stimulation immediately abolishes the gastric motor and neurohormonal activity during the digestive and inter-digestive periods[23] (Table 2).

6 | REGULATION OF GASTRIC MOTILITY AND EMPTYING

Gastric motility is regulated by the neural circuits that affect the activity of its final target, the smooth muscles. The interstitial cells of Cajal (ICC) may also be involved in the control of gastric emptying in multiple ways, including afferent mechanosensing,[28] certain types of neuromuscular transmissions (NMT),[29,30] and phasic contractions in the antrum.[31,32] However, the multifunctional role of ICC has been questioned.[33]

7 | NEURAL CONTROL OF GASTRIC MOTILITY

It is now generally accepted that autonomic nerves regulate gastric motility.[34-36] Traditionally, parasympathetic and sympathetic motor nerves were thought to exert an excitatory and inhibitory effect on the stomach, respectively. However, studies showed that sympathetic nerves do not have an important role in physiological regulation of gastric motility, while the vagus nerves exert both inhibitory and excitatory effects on the stomach via the gastric inhibitory vagal motor circuit (GIVMC) and a gastric excitatory vagal circuit (GEVMC).[37-39]

Gastric inhibitory vagal motor circuit consists of preganglionic cholinergic and postganglionic non-cholinergic inhibitory neurons. The GEVMC consists of preganglionic cholinergic and postganglionic cholinergic neurons. Moreover, the GIVMC and GEVMC are regulated by other connected neurons and, together, they constitute the gastric inhibitory vagal circuit (GIVC) and a gastric excitatory vagal circuit (GEVC), respectively. Because the neurons of the same chemical nature may be present at different locations of the circuit and even in two opposing circuits, we have identified them by their location, chemical nature, and the functional circuitry in the descriptive table (Table 3).

TABLE 3 Abbreviated identity of neurons involved in gastric emptying as identified by three parameters, namely, anatomic location, chemical nature, and their participation in the gastric inhibitory or gastric excitatory and hunger or satiety neural circuits

	Triangular parameters		
Neuron identity	Location	Chemical nature	Neural circuit
NG-GLUT-i	Nodose Ganglion	Glutaminergic	Gastric inhibitory
NTS-CC-i	Nucleus tractus solitarius	Catecholaminergic	Gastric inhibitory
NTS-GLUT-e	Nucleus tractus solitarius	Glutaminergic	Gastric excitatory
NTS-GABA-e	Nucleus tractus solitarius	Gamma-aminobutyric acid-ergic	Gastric excitatory
NTS-PPG-i	Nucleus tractus solitarius	Pre-proglucagon	Gastric inhibitory
NTS-POMC-s	Nucleus tractus solitarius	Pro-opiomelanocortin	Satiety
DMV-C-e	Dorsal motor nucleus of vagus	Cholinergic	Gastric excitatory
DMV-C-i	Dorsal motor nucleus of vagus	Cholinergic	Gastric inhibitory
DMV-GABA-e	Dorsal motor nucleus of vagus	Gamma-aminobutyric acid-ergic	Gastric excitatory
MP-C-e	Myenteric Plexus	Cholinergic	Gastric excitatory
MP-NANC-i	Myenteric Plexus	Non-cholinergic, non-adrenergic	Gastric inhibitory
H-POMC-s	Hypothalamus	Pro-opiomelanocortin	Satiety
H-NPY/GABA-h	Hypothalamus	Neuropeptide Y/ Gamma-aminobutyric acid	Hunger
H-Gh-h	Hypothalamus	Ghrelin	Hunger
H-OREX-h	Hypothalamus	Orexigenic	Hunger
H-ANOREX-s	Hypothalamus	Anorexigenic	Satiety

8 | GASTRIC INHIBITORY VAGAL MOTOR CIRCUIT (GIVMC)

Gastric inhibitory vagal motor circuit consists of preganglionic cholinergic neurons in the DMV (DMV-C-i) and postganglionic, non-adrenergic non-cholinergic (NANC) inhibitory neurons in the myenteric plexus (MP-NANC-i) (Figure 3A). The DMV-C-i neurons are distinct from the DMV-C-e neurons and are located in rostro-lateral and caudomedial areas of the DMV.[40] Moreover, DMV-C-i neurons are segregated into distinct groups and may have different chemical markers, so that they regulate the different regions of the stomach separately.[41]

Motor axons of the DMV-C-i neurons travel in the vagus nerve and exert a tonic inhibitory effect on the lower esophageal sphincter[42] and the stomach.[43,44] The tonic inhibitory neural effect is also evidenced by the observation that an isolated guinea pig stomach is spontaneously contracted so that small gastric distension causes a steep increase in intragastric pressure and increases the amplitude of pressure waves. The resting tonic contraction may be due to the removal of tonic gastric inhibitory vagal influence. In contrast, larger distension volumes cause a decrease in the intragastric pressure indicating that the response is mediated by a local inhibitory reflex.[45]

Vagal motor fibers to different regions of the stomach assemble in different branches of the vagus that innervate the gastric fundus, corpus, and antrum and the pyloric sphincter.[46] Various types of vagotomy performed for the treatment of peptic ulcer disease have provided important information on vagal control of motility of different parts of the stomach. Proximal gastric vagotomy leads to vagal denervation of the fundus and the proximal corpus and impairs receptive relaxation and accommodation of the fundus. These changes increase the fundic tone and lead to a fast emptying of liquids.[43] Because proximal vagotomy spares the distal stomach, a regular pattern of trituration, sieving, and solid emptying is preserved. Truncal vagotomy and selective vagotomy denervate most of the stomach including the pylorus. Denervation of the pylorus causes a decrease in compliance and loss of relaxation that leads to pyloric obstruction and gastric stasis.[44] On the other hand, stimulation of vagal motor fibers has been shown to decrease pyloric resistance.[47] Clinically, truncal or selective vagotomy is always combined with pyloroplasty in the surgical treatment of peptic ulcer, to prevent gastric stasis.

The vagal motor axons of DMV-C-i neurons synapse onto the postganglionic, MP-NANC-i neurons via nicotinic (N) and muscarinic (M1) receptors.[48] Stimulation of the MP-NANC-i neurons relaxes the smooth muscle by releasing NO, ATP, and VIP.[49,50] $NO^{\cdot}$ causes

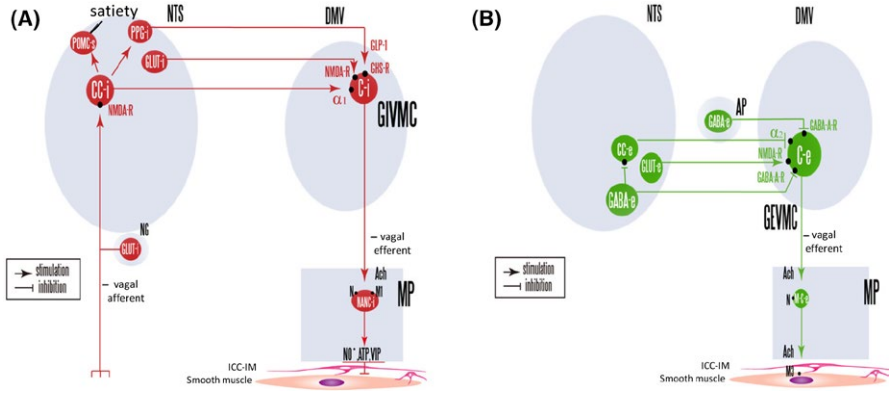

FIGURE 3 A simplified gastric inhibitory vagal circuit (GIVC) and the gastric excitatory vagal circuit (GEVC). (A) The GIVC includes GIVMC and its inputs. GIVMC consists of preganglionic DMV-C-i neuron and postganglionic, NANC inhibitory neuron in the myenteric plexus (MP-NANC-i). See text for details of the neurotransmission. The DMV-C-i neurons receive excitatory input directly from the NTS-CC-i neurons via the α1-receptors and through NTS-PPG neurons via GHSR or GLP-1 receptors. The NTS-CC-i neurons receive glutaminergic input from low-threshold vagal afferents whose neurons are in the nodose ganglion (NG). (Arrow—stimulation; flat—inhibition). (B) The GEVC includes GEVMC and its inputs. GEVMC consists of preganglionic DMV-C-e neurons and postganglionic, cholinergic excitatory myenteric plexus (MP-C-e) neurons. DMV-C-e neurons receive strong inhibitory input from NTS-GABA-e neurons and NTS-CC-e neurons, and excitatory input from NTS-GLUT-e neurons. The NTS-GABA-e, NTS-CC-e, and NTS-GLUT-e neurons are interconnected and send integrated inhibitory input to the DMV-C-e neurons. NTS-CC neurons also send inhibitory input to DMV-C-e neurons via the α2-receptors. The inhibitory inputs from the NTS to DMV-C-e suppress spontaneously active DMV-C-e and cause gastric relaxation. On the other hand, suppression of the NTS-GABA neurons NTS-CC-i disinhibits the spontaneously active DMV-C-e neurons leading to gastric excitation and fast gastric emptying as in acute hypoglycemia. See text for other details. (Arrow—stimulation; flat—inhibition)

smooth muscle relaxation in part by causing membrane hyperpolarization (nitrergic IJP) via sGC-cGMP signaling; ATP causes relaxation mainly by causing membrane hyperpolarization via P2Y1 receptors-SK channel signaling (purinergic IJP); VIP acts by increasing intracellular cAMP.[51] Out of these different inhibitory transmissions, muscle relaxant effect of NO· is most prominent.[52-54]

Stimulation of nitrergic neuromuscular transmission (NMT) in the pressure and peristaltic pumps causes slow gastric emptying, while its suppression causes fast gastric emptying in the digestive period.[55,56] On the other hand, loss of nitrergic NMT in the tubular pylorus causes delayed gastric emptying in the inter-digestive period.[27] ICC-IM and PDGFRα+ fibroblasts have been proposed to be necessary for nitrergic and purinergic NMT, respectively.[29,57] However, this proposal is open to question.[56,58]

The regulatory part of the GIVC includes vagal afferents and second-order neurons in the NTS for vagovagal reflex and other neurons that provide input to the NTS neurons. Esophagogastric relaxation and gastric accommodation reflexes are well-studied gastric inhibitory vagovagal reflexes.[40,52-54] The vagal afferents have their cell bodies in the nodose ganglion. Originally, neural input to the DMV-C-i was thought to be from vagal afferents leading to monosynaptic vagovagal reflexes. However, it is now clear that the vagal afferents do not directly synapse on the DMV-C-i neurons but project onto second-order neurons in the NTS (Figure 3A).

The vagal afferents provide glutaminergic excitatory input to the NTS-CC-i neurons.[59] The afferent terminals are a site of action of multiple hormones that act presynaptically to modulate these synapses.[60,61] The NTS-CC-i neurons inhibit gastric motility by multiple pathways,[62] including direct stimulation of DMV-C-i neurons via α1-receptors[63] and indirectly via stimulation of NTS-PPG neurons that release glucagon-like peptide-1 (GLP-1) onto the DMV-C-i neurons.[64] Stimulation of NTS-CC-i neurons also inhibits DMV-C-e neurons via α2-catecholaminergic receptors and further enhances the gastric inhibitory effect.[63] It has been estimated that the GIVMC mediates fundic relaxation in the esophagogastric reflex.[53]

9 | GASTRIC EXCITATORY VAGAL MOTOR CIRCUIT (GEVMC)

Gastric excitatory motor circuit (GEVMC) consists of preganglionic cholinergic neurons (DMV-C-e) and postganglionic cholinergic (MP-C-e) neurons (Figure 3B). The DMV-C-e neurons of the GEVMC are distinct from the DMV-C-i neurons of the GIVMC.[37] The DMV-C-e neurons are located in the more rostral and medial divisions of the DMV and are spontaneously active and may cause tonic excitation of the stomach muscle.[40] Their motor axons are carried in the vagus nerve in the company of the fibers of the GIVMC and vagal afferents. The preganglionic efferent fibers synapse on the MP-C-e neurons involving nicotinic receptors. The postganglionic excitatory myenteric neuron releases acetylcholine to contract the smooth muscles via M3 receptors. ICC-IM has also been proposed to be included in the transduction of cholinergic neural signals to smooth muscles.[29,30,32,65] However, the role of ICC-IM in cholinergic NMT is questionable.[33,58,66]

The vagal excitatory circuits are a dominant regulator of gastric acid secretion and hormonal release, but GEVMC plays a less dominant role in gastric motility.[36] Cholinergic excitatory motor responses are usually masked by the stronger inhibitory responses.[67] Moreover, cholinergic responses are highly dependent on the sensitivity of the smooth muscle that is related to the activity of the RhoA/ROCK signaling.[51,68]

The regulatory part of the GEVC includes GABAergic neurons that exert a tonic inhibitory influence on the DMV-C-e neurons and neutralize their excitatory tonic effect.[69,70] Stimulation of the NTS-GABA-e neurons suppresses the activity of DMV-C-e leading to a decrease in the gastric tone and the motility of the gastric corpus and antrum.[71] A recent study using optogenetic stimulation suggested that somatostatin-positive GABA neurons in the DMV are responsible for the gastric inhibitory effect of vagus-mediated gastric antral motility.[72] However, further studies are needed to elucidate the distinct roles of GABA neurons in NTS and DMV in gastric motility. NTS-GABA and NTS-non-GABA inhibitory neurons and NTS-GLUT excitatory neurons exert an inhibitory and excitatory effect, respectively, on the DMV-C-e neurons.[73]

Moreover, within the NTS, the GABA, non-GABA, and GLUT neurons are interconnected.[74] NTS-CC-e neurons may also act to inhibit DMV-C-e neurons via the α2-receptors.[62,75] Thus, NTS neurons exert a precise inhibitory regulation of the GEVC. DMV-C-e neurons also receive GABAergic inhibitory input from area postrema.[76] Interestingly, vagal afferent input to GEVMC has not been described.

A variety of neurotransmitters and endogenous chemicals may exert different effects on vagal circuits, based on the receptor type and the neural input. For example, dopamine may use either stimulatory effect via the dopamine 1 (DA1) receptors or inhibitory effect via the dopamine 2 (DA2) receptors on the DMV neurons of the GEVC.

Moreover, DA2 receptor-mediated effect is more prominent than the DA1 receptor-mediated effects.[77] Thus, stimulation of dopaminergic projections of substantia nigra pars compacta (SNpc) causes some gastric excitation due to stimulation of DA1 receptors on the DMV-C-e neurons.[77] However, gastric inhibitory effect and delayed gastric emptying in Parkinson's disease associated with loss of dopamine in substantia nigra may not be due to loss of DA1 receptor-mediated excitatory effect on the DMV-C-e neurons but may be due to the increase in dopaminergic input from other neurons that primarily act to stimulate inhibitory DA2 receptors.[77] Moreover, in animal models of Parkinson's disease a decrease in DA1 and increase in DA2 receptors in the DMV have been reported.[78] Thus, degeneration of SNpc-DMV dopaminergic pathway neurons in Parkinson's disease may cause delayed gastric emptying primarily due to a gain of DA2 receptor-mediated neurotransmission in the DMV.[79] It is intriguing to consider that prokinetic agents such as DA2 receptor antagonists may accelerate gastric emptying in Parkinson's disease.[80] Although domperidone does not readily cross blood-brain barrier, it may act on areas that have deficient blood-brain barrier.[81]

10 | MOTOR BEHAVIOR OF DIFFERENT SEGMENTS OF THE STOMACH

The different segments of the stomach may be regulated by distinct sub-circuits of the GIVC and GEVC, the nature of their smooth muscles and presence of the ICC-MY.

The smooth muscles of the pressure pump, the peristaltic pump, and the grinder-filter have distinct mechanical behaviors. Smooth muscle of the pressure pump, fundus, and proximal corpus is primarily of tonic phenotype. In response to cholinergic stimulation, fundic smooth muscle elicits a strong tonic contraction.[51,68] The muscles of the peristaltic pump, distal corpus, and the proximal antrum are primarily of phasic phenotype, and cholinergic stimulation elicits phasic contractions.[82] Muscle of the pyloric complex possesses both phasic and tonic muscles.

The phasic muscles are paired with the myenteric type of interstitial cells of Cajal (ICC-MY). ICC-MY generate propagates electrical slow waves in the distal stomach at a rate of 3-5 per minute. That serve to set the pace for the phasic contraction and have been called pace-setter potentials. The pylorus exhibits nearly simultaneous and strong slow waves that are associated with forceful contractions.[83]

Slow waves recorded by surface electrodes in vivo have often been assumed to represent phasic contractions. However, it has been reported that (a) extracellularly recorded slow waves in vivo may not represent true slow waves recorded intracellularly,[84] (b) slow waves recorded by surface electrodes are strongly influenced by neural stimuli and may not represent mechanical contractions,[85,86] and (c) Klotho-deficient progeric mice that have a profound loss of ICC and reduced amplitude of slow waves manifest no change in gastric emptying of solids.[87] Therefore, the role of ICC-MY and the slow waves recorded by surface electrodes remains unclear.

11 | HORMONAL CONTROL OF GASTRIC MOTILITY

One of the most characteristic features of normal gastric emptying is its large variability, depending on the chemical composition of the food (Figure 1). The effect of different foods on gastric emptying is in large part due to the hormones released from the gastrointestinal tract that provides feedback regulation of gastric emptying. These hormones are released from the stomach, intestines, pancreas, and other tissues and act at various levels of the neural circuits including vagal afferents, NTS, area postrema (AP), preganglionic vagal neurons in the DMV, and myenteric plexus and the smooth muscle. It is noteworthy that the dorsal vagal complex (DVC, including NTS, AP, and DMV) is located outside the blood-brain barrier, has a large network of fenestrated capillaries, and contacts specialized neurons lining the ependymal layer of the central canal and fourth ventricle.[81] Some of these hormones, along with other mediators, act on other control centers to coordinate gastric motility with satiety, food intake, and energy balance. Some GI hormones serve as a brake to slow gastric emptying and are called “braking hormones,” while others serve to accelerate gastric emptying and are called “accelerating hormones” (Table 4).

12 | GASTRIC “BRAKING” HORMONES

Ingestion of a meal causes a release of a large number of hormones that act to put “brakes” on gastric emptying.[88] These hormones are active during the digestive period and include cholecystokinin (CCK), GLP-1, and leptin.

TABLE 4 Hormones that cause slow gastric emptying and that cause fast gastric emptying

Slow gastric emptying	Fast gastric emptying
Cholecystokinin	Ghrelin
Leptin	Motilin
Glucagon-like peptide-1	
Glucagon	
Oxyntomodulin	
Peptide YY	
Gastrin-releasing peptide	
Enterostatin	
Pancreatic amylin	
Pancreatic polypeptide	

Cholecystokinin is a prototype of gastric braking hormones. It is released from neuroendocrine cells in the duodenum by stimuli such as hydrochloric acid, amino acids, and fatty acids. CCK acts to stimulate the GIVC at multiple levels. CCK stimulates vagal afferent endings of the vagal inhibitory circuit in a paracrine fashion,[89,90] may act on nodose ganglion,[91] and may enhance synaptic neurotransmission at the vagal afferent second-order NTS-CC-i neurons by enhancing release of glutamate in the NTS.[89,92] Furthermore, intraperitoneal application of CCK-8 induces c-FOS immunoreactivity in the catecholaminergic (CC), pro-opiomelanocortin (POMC), and pre-proglucagon (PPG) neurons.[93] CCK stimulation of the NTS-CC-i neurons may, in turn, stimulate NTS-POMC and NTS-PPG neurons. Thus, CCK may excite DMV-C-i neurons using multiple pathways including the projections of the NTS-CC-i neurons via the α1-receptor[89,94] and projections of the NTS-PPG neurons via GLP-1. CCK also exerts its gastric inhibitory effect by stimulating the myenteric non-adrenergic non-cholinergic (NANC) inhibitory neurons[95] (Figure 4A).

CCK also interacts closely with GLP-1 and bile salts. CCK releases GLP-1 that is an important gastric inhibitory hormone. It has been reported that entry of chyme in the gut releases nesfatin-1 that stimulates CCK secretion that causes gallbladder emptying and rise in bile salts.[96] Bile salts stimulate Takeda G-protein-coupled receptor-5 (TGR5) on the basolateral aspect of the enteric endocrine L cells to elicit GLP-1 secretion.[97] CCK activation of NTS-CC-i neurons may also inhibit DMV-C-e via the α2-adrenergic receptors. All these actions of CCK lead to robust gastric inhibition and slowed gastric emptying.

Gastric emptying is also slowed by the products of posttranslational modifications of pre-proglucagon, which act to slow gastric emptying and serve as braking hormones.[98] In the pancreatic alpha cells, these products include glucagon, proglucagon 1-61, and the so-called major proglucagon factor (MPGF, ie, fused GLP-1 and GLP-2). Following ingestion of a meal, the L cells of the intestinal wall and PPG neurons in the NTS produce pre-proglucagon gene products including GLP-1 and its amide, GLP-2, oxyntomodulin, and glicentin. GLP-1 is the most studied in this group. However, GLP-1 is rapidly degraded by N-terminal degradation by dipeptidyl peptidase IV (DPP IV, CD26). DPP IV inhibitors and DPP IV-resistant incretin analogs have been used to prolong its activity.[99]

GLP-1 released from the intestines acts to stimulate vagal afferents that stimulate the second-order NTS-CC-i neurons that activate DMV-C-i neurons. GLP-1 released from NTS-PPG neurons also

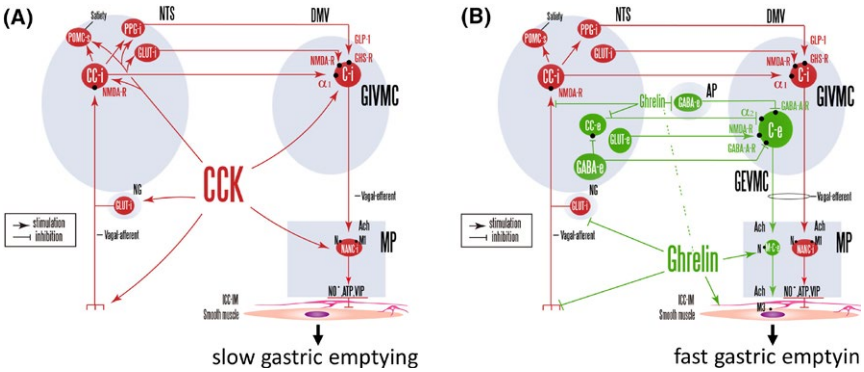

FIGURE 4 Main sites of action of CCK and ghrelin. (A) Cholecystokinin (CCK) is a prototype breaking hormone. It acts to stimulate vagovagal circuit at multiple levels. CCK stimulates vagal afferents endings by paracrine effect and enhances glutamate release from the vagal afferent endings projecting onto NTS-CC-i neurons. CCK also directly or indirectly stimulates NTS-CC-i neurons, PPG-i neurons, and NTS-POMC-S neurons. CCK stimulation of NTS-CC-i neurons activates DMV-C-i via the α1-adrenergic receptor; stimulation of the NTS-PPG-i neurons via the GLP-1 receptor on the DMV-C-i. CCK has also been shown to directly stimulate MP-NANC-i neurons, and may also stimulate DMV-C-i neurons. Thus, CCK acts at multiple sites to stimulate GIVC. Stimulation of NTS-CC-i neurons also inhibits DMV-C-e neurons via the α2-adrenergic receptors. Thus, CCK also acts to inhibit GEVC. All these actions further augment the inhibitory effect of CCK on the gastric muscle. CCK also stimulates NTS-POMC-s neurons to generate satiety signals. (Arrow—stimulation; flat—inhibition). (B) Ghrelin is a gastric accelerating hormone. Ghrelin acts at multiple central and peripheral sites to stimulate gastric motility. Centrally, ghrelin inhibits NTS-CC-i neurons thereby inhibiting DMV-C-i. Ghrelin also inhibits NTS-CC-e to disinhibit DMV-C-e neurons. Ghrelin also disinhibits DMV-C-e neurons by inhibiting AP-GABA-e neurons that project onto DMV-C-e neurons. Ghrelin also acts on myenteric plexus and the smooth muscle. All these actions lead to strong gastric excitation. (Arrow—stimulation; flat—inhibition)

stimulates DMV-C-i neurons.[89] By stimulating NTS-CC-e, GLP-1 may also inhibit DMV-C-e neurons. These multiple actions account for a strong inhibitory effect of GLP-1 on gastric motility.[89,100] In functional studies, intravenous GLP-1 has been shown to retard gastric emptying and decrease the number and volume of flow pulses in the trans-pyloric flow. This was associated with an inhibition of antropyloric pressure waves, but stimulation of isolated pyloric pressure waves, and an increase in basal pyloric tone.[101] Interestingly, decreased gastric contraction but increased intestinal contractions have been reported to cause delayed gastric emptying in response to nutrients.[21]

Other pancreatic hormones such as insulin and islet amyloid peptide (amylin) are co-secreted from the beta cells. Both these hormones act to slow gastric emptying and reduce appetite. Pancreatic polypeptide (PP) is secreted by PP cells of the pancreas during the cephalic phase of gastric acid secretion via cholinergic excitatory pathway.[102] PP has been shown to act on the area postrema and stimulate a gastric inhibitory vagovagal reflex and slow gastric emptying.[76]

Gastric leptin is released from the chief cells along with pepsin in the gastric juice by protein load and vagal stimulation. It is reprocessed in the small bowel to be released as a hormone. Leptin may produce its peripheral effect via the CCK1 receptors. However, the primary source of leptin is white fat cells (adipokine leptin). Gastric leptin slows gastric emptying in response to a protein meal. Secretion of adipokine leptin is constitutive and exerts its primary effect on hypothalamic nuclei to inhibit food intake and gastric emptying.[103] It is interesting to note that intragastric infusion of nutrient rapidly inhibits hunger-promoting, agouti-related peptide/neuropeptide Y (AgRP/NPY, orexigenic) neurons in awake mice. This inhibition is proportional to the number of calories but independent of the type of food and is mediated by CCK, peptide YY, and 5-hydroxytryptamine (5HT). Leptin induces a slow modulation that develops over hours and is required for the inhibition of feeding.[104]

13 | GASTRIC "ACCELERATING" HORMONES

Ghrelinand motilin act to accelerate gastric emptying and are released in the inter-digestive (fasting) period.[105] No gastric accelerating hormones are released in the digestive period. Ghrelin is released from G cells in the stomach and the ghrelin-containing neurons in the hypothalamus. Ghrelin acts on the growth hormone secretagogue receptor (GHSR) to stimulate the release of growth hormone. Ghrelin increases food intake, fat deposition, and weight gain.[106] It is a primary stimulant of appetite and is called the "hunger hormone" (Table 4).

Ghrelin serves as a neurotransmitter as well as a hormone, exerts its effects centrally as well as peripherally, and acts on afferent as well as efferent pathways (Figure 4B). Ghrelin inhibits vagal afferent activity at the level of the sensory endings,[107] nodose ganglion,[108] and the afferent terminal to NTS-CC synapses.[59,61] Suppression of NTS-CC neurons leads to inhibition of the DMV-C-i and disinhibition of DMV-C-e neurons. Ghrelin also disinhibits DMV-C-e neurons by activating AP-GABA neurons[109,110] and facilitates excitatory transmission to DMV-C-e neurons.[111] Moreover, ghrelin also directly stimulates MY-C-e neurons. These actions lead to the gastric stimulatory effect of ghrelin. Functional in vitro studies have shown that ghrelin augments electrically stimulated contractions of fundic strips in mice.[112] In vivo, ghrelin increases gastric myoelectrical activity and gastric emptying in the rats.[113] Ghrelin activates phase II activity in the antrum of the fasting stomach by a central action.[111] The peripheral action of ghrelin facilitates motilin to induce the activity in front of the MMC.[114] By inhibiting the vagal afferents, ghrelin also suppresses anorexigenic signals and stimulates hunger at the NTS and hypothalamic levels.[107,115]

Motilin is released from M cells during the inter-digestive phase.[114] Motilin release is due to duodenal alkalization that occurs as a compensatory response to duodenal acidification during the digestive phase. Acidification of the duodenum causes a release of prostaglandin E2 (PGE2) and 5HT. PGE2 inhibits further acid secretion and contributes to duodenal alkalization. 5HT acts on 5HT4 receptors to cause a release of duodenal bicarbonate that further alkalinizes the duodenal mucosa. 5HT4 receptor stimulation also causes duodenal contractions that activates a gastro-stimulatory ascending vagal reflex.[19]

Motilin acts on multiple sites including the myenteric neurons and smooth muscles in a species-dependent fashion.[116] Its action on myenteric plexus neurons initiates phase III of the gastric MMC that promotes gastric emptying of indigestible food residues. Phase III of the MMC is strongly inhibited by the gastric inhibitory vagovagal reflex that is activated upon ingestion of food. It is worth pointing out that rodents do not exhibit typical MMC pattern because they lack motilin owing to a defective motilin gene.[117] However, dogs and the house musk shrew (*Suncus murinus*) exhibit MMC pattern similar to that seen in humans. Therefore, these animal species have been used to investigate the mechanism of action of ghrelin and motilin in MMC.[114]

14 | LINKING GASTRIC EMPTYING TO SATIETY SIGNALS, FOOD INTAKE, AND GLUCOSE METABOLISM

Gastric emptying is linked to sensations of satiety, appetite, and hunger and their hedonic aspects as well as to chronic food intake and energy homeostasis. This linkage involves connections of the GIVC and GEVC with the NTS-CC-i and NTS-CC-e neurons connected with satiety- and hunger-associated neural pathways, respectively, in the hypothalamic, limbic, and cortical areas of the brain[118] and the NTS.[94,119]

15 | CONCLUSION

The primary function of the stomach is to prepare ingested food into chyme and provide regulated delivery into the small bowel that is

measured as gastric emptying. Earlier studies had identified two remarkable characteristics of gastric emptying: (a) ability to regulate the timing and rate of emptying of ingested food of different physical compositions; and (b) ability to regulate emptying based on the caloric density of food. Studies on the biomechanics of gastric emptying revealed that activity of different anatomic parts of the stomach was integrated to form functional "pressure" and "peristaltic" pumps and a grinder-filter that played well-defined roles in gastric emptying. The peristaltic pump is mainly involved in gastric emptying of solids.

The pattern and the rate of gastric emptying have been shown to be regulated by two parallel circuits, the gastric inhibitory vagal motor circuit (GIVMC) and the gastric excitatory vagal motor circuit (GEVMC), which mediate gastric inhibition and excitation, respectively. The GIVMC includes preganglionic cholinergic neurons in the DMV and the postganglionic NANC inhibitory neurons, in the myenteric plexus. The GEVMC includes distinct gastric excitatory preganglionic cholinergic neuron in the DMV and postganglionic excitatory, cholinergic neurons in the myenteric plexus. It was proposed but remains unproven that ICC-IM were required to transduce nitrergic and cholinergic neural signals to the gastric smooth muscles. The circuits for different parts of the stomach are distinct, so that different parts of the stomach can be differentially regulated. Currently, ongoing studies also show that some intestinal and pancreatic hormones released during the digestive period inhibit gastric motility by stimulating the GIVC and inhibiting the GEVC.

On the other hand, in the inter-digestive period, hormones ghrelin and motilin and motilin act by stimulating gastric pumps and inhibiting pyloric contraction. Studies have also shown that the GIVC is linked to anorexigenic neurons in the NTS and hypothalamus, and GEVC may be linked to the orexigenic signals. Therefore, neurohormonal controls link disorders of gastric emptying with satiety signal, food intake, and energy metabolism as well as postprandial hyperglycemia in the pathogenesis and management of diabetes mellitus.

ACKNOWLEDGMENTS

We thank Maryrose Sullivan, PhD, and Vivian Cristofaro, PhD, for their critical comments and helpful suggestions. We also appreciate Frances Achee, PhD, for administrative help.

CONFLICT OF INTEREST

The authors report no conflict of interest relevant to this article.

AUTHOR CONTRIBUTIONS

RKG conceived and designed the study and wrote the manuscript; YMG made all the illustrations, conducted literature search, and wrote this review; HM provided critical input in the organization and writing of this review.

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How to cite this article: Goyal RK, Guo Y, Mashimo H. Advances in the physiology of gastric emptying. *Neurogastroenterol Motil*. 2019;31:e13546. https://doi.org/10.1111/nmo.13546