

Overview of Enteric Neurobiology

1.1 THE ROLE OF THE GUT

At the beginning of the 20th century, Ramón y Cajal revealed the intricacies of the structure of the central nervous system. The nerve plexuses in the wall of the gut were described by Leopold Meissner and Georg Auerbach in the mid-19th century, but their function remained obscure for another hundred years, while notable advances were made in the physiology of the central nervous system. The principal reason for this relative obscurity was that there were no obvious functions that could be ascribed to the enteric nerves. In contrast, the motor and sensory functions controlled by the central nervous system — perception and bodily movement — are part of universal human experience and readily susceptible to study. In health, apart from occasional minor discomforts, the only conscious events that can be related to the digestive system, are the ingestion of food and fluid, and the act of defecation; moreover, these activities appear to be modulated by social and cultural rather than biological constraints. The elucidation of gut function only became possible when advances in technology enabled dynamic imaging of the gut and sampling of its content.

The gut is a specialized region of the body surface that, being an invaginated tube through the body, is protected from the external environment. Unlike the skin, the surface of the gut is permeable, allowing nutrients and water to be absorbed to provide energy substrates to the organism, and to maintain fluid balance. In terrestrial species, for whom food and water are only intermittently available, the gut tube is also a storage device that allows the absorption of solutes and fluid over a much longer period of time than

the relatively brief periods available for the ingestion of food and water. In all species, the gut tube is normally closed at each end by muscular structures that only relax proximally for the ingestion of nutrients and distally for the expulsion of waste. But it is important to remember that the lumen of the digestive tube is external to the body. It is possible to insert a probe into one end of the gut and advance it to the other end without breaching the surface of the body. But the enclosure of the gut cavity within the body confers thermal equilibration of the gut contents with the “milieu interieur,” and protection from mechanical damage to a mucosal surface that is, in parts, highly permeable.

There is a wide variation in the gross anatomy of the digestive tract between species, reflecting varying habitats and diets, but there are also some common properties. In vertebrate species, the abdominal cavity is separated from the mouth by the thorax, hence the first part of the gut is a transit segment. This empties into a digestive region, where mechanical and chemical breakdown of nutrients is assisted by the addition of fluid and enzyme secretions. The final section of the digestive tube stores the residue for the final extraction of water and electrolytes and the eventual expulsion of solid waste.

The nomenclature of the different regions of the human digestive tract is shown in Fig. 1.1. The esophagus is the conduit traversing the thorax from the mouth to the stomach. The stomach is the digestive vat, and has two distinct regions. The corpus is the storage region, where food accumulates and hydrochloric acid and enzymes are secreted from the mucosal lining into the cavity. The antrum is the pump that delivers gastric contents into the small intestine, which is the main absorptive region. The proximal, middle, and distal portions of the small intestine are, respectively, the duodenum, jejunum, and ileum. There are no structures in the wall of the gut that mark the limits of the three divisions, only a gradual change in mucosal structure. Conventionally, the junction of the duodenum and jejunum is located at the ligament of Treitz, where the otherwise freely mobile intestine is anchored by fascia, but there is no stepwise change in the anatomy of the bowel at this point. There is no defined location for the junction between jejunum and ileum, only a gradual change in mucosal structure along the entire length of the small intestine. Finally, the large intestine is a capacious cavity for the storage of food residues; the colon is the site of bacterial degradation of

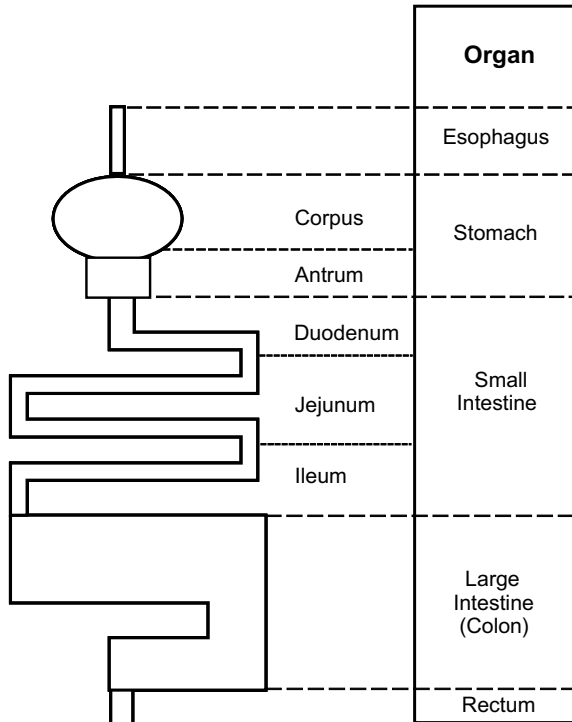


Fig. 1.1 Schematic representation of the anatomy of the human digestive tract.

the remaining solids, and of the final extraction of water and electrolytes to create solid feces. The final segment of the large intestine is the rectum; it is for the most part a potential cavity, except when the propulsion of feces from the distal colon provides the stimulus for defecation.

1.2 REGIONAL FUNCTION IN THE HUMAN GUT

Unlike the locomotor system, where we have detailed knowledge of physical activity, both visually and through proprioception, the gastrointestinal system provides few clues to its owner about its operations. Swallowing and defecation, respectively the propulsion and expulsion of substances, are voluntary behaviors, but the progress and transformation of material between these two acts are, for the uninformed, hidden mysteries. In upright humans, the mouth is above the anus, and children often make the naïve assumption

that gravity is important in the transit of food through the body, but gravity is not a propulsive force in the digestive tract. Propulsion is determined by the two layers of smooth muscle that surround the entire digestive tract. The inner layer of circular muscle can contract to produce a constriction of the gut cavity, while contraction of the outer layer of longitudinal muscle can reduce the length of a gut segment. In general, all circular contractions move in a caudad direction; the distance traversed by a contraction varies between a few millimeters and many centimeters. The different functions of the segments of the digestive tube are summarized in Fig. 1.2. The duration of residence of ingested material in each segment differs greatly, and is related to the transformations that take place in each segment.

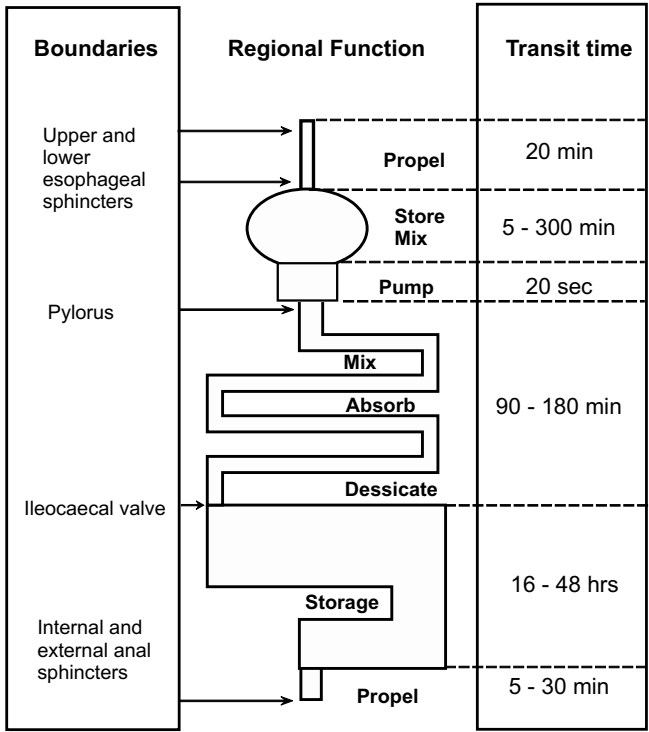


Fig. 1.2 Summary of the function of the digestive tract. The main function of the different regions (the central column); the location of the sphincters of the gut (the left-hand column), and the duration of transit of gut content through the different regions (the right-hand column).

Transit through the esophagus into the stomach is rapid — a matter of seconds — and is accomplished via peristalsis: a circular muscle contraction occluding the cavity and preceded by a phase of relaxation, that traverses the entire esophagus. The caudal end of the esophagus is normally closed by a muscular structure, the lower esophageal sphincter, but the intrinsic innervation of the muscle ensures that the sphincter relaxes to allow the swallowed bolus of solid or liquid to pass into the stomach.

The stomach has two functional divisions: corpus and antrum. The distal end of the antrum leads to the duodenum through the pylorus which is also a smooth muscle sphincter. To understand the mechanical function of the stomach, it is important to appreciate that the corpus and antrum have different properties. The corpus is a mixing chamber that delivers gastric content to the antrum; the latter is essentially a bidirectional pump. As soon as material is delivered from the esophagus, regular contractions sweep down the stomach as far as the pylorus every 20 seconds. These contractions are not powerful enough to occlude the cavity of the corpus, but they serve to mix ingesta and secretions, and propel content into the antrum. Compared to the corpus, the antrum is a narrow tube, and is occluded by the contraction wave, while at the same time, the pyloric sphincter briefly relaxes. During the antral contraction, a portion of content is propelled as a bolus through the pylorus into the first part of the duodenum, while the remainder is forced back into the corpus and the pylorus closes. This cyclical activity continues until all the ingested content has been emptied from the stomach. Effectively, only a few milliliters of content are delivered with each gastric contraction. Gastric emptying starts almost as soon as a meal arrives, but complete emptying of a meal, depending upon its physicochemical composition, requires an average of about five hours.

The colon is the reservoir for the accumulation of non-absorbed solids, and for the recovery of most of the remaining water and electrolytes. This is essentially a process of desiccation, in which fluid content is transformed into solid feces. This is a slow process; propulsion of feces through the colon may require 24–48 hours. The final internal destination of feces is the rectum, which is filled by infrequent high amplitude peristaltic contractions of the distal colon. Distension of the rectum by feces or by gas from bacterial digestion or swallowed air is a conscious perception, and results in the urge to release gas as flatus, or to expel feces in the act of defecation. Thus, while

the transit of feces through the colon is slow, the residence of material in the rectum is brief, assuming that the “call to stool” is heeded. Constipation — fecal retention — is often the consequence of the individual failing to respond to the stimulus of rectal filling.

It is important to bear in mind that the major internal sphincters of the digestive tube — lower esophageal, pyloric, and ileocecal — are not, as was once thought to be the case, structures that regulate forward flow. Their function is to prevent retrograde flow (reflux) of content from one segment to the preceding segment because of the damage that can be inflicted. Thus, the acid contents of the stomach damage the mucosal lining of the esophagus, and bile damages the gastric mucosa, while migration of material from the colon into the ileum leads to bacterial overgrowth of the small bowel.

This account of regional gut function is no more than a brief summary of a complex series of processes; a detailed narrative of the variables and mechanisms that govern the system would fill an entire textbook. Nevertheless, it should serve to show that the digestive tract is a complex organ system, capable of responding to variable inputs of food and fluid with the efficient extraction of nutrients and the exclusion of waste. Moreover, the system is able to deliver ingested solids and liquids that range between pure water and complex solids to the permeable surface of the digestive tube at a rate that does not overwhelm the absorptive processes. Nothing is wasted, and that includes the large volume of body water and electrolytes that is secreted into the gut. Appropriate propulsive motor activity of the muscular wall of the digestive tube is clearly a key component of this adaptive ability, and as with other motor functions of the body, this requires neural control.

1.3 THE INTRINSIC INNERVATION OF THE GUT

The intrinsic innervation of the gut consists of two networks of neurons that entirely surround the bowel (Fig. 1.3). The myenteric plexus (Auerbach’s plexus) is located in a plane of connective tissue between the outer longitudinal muscle and the inner circular muscle, and the submucosal plexus (Meissner’s plexus) lies between the circular muscle and the submucosal layer. Both have similar architecture; they consist of a network of ganglia interconnected by axon bundles. The ganglia contain the cell bodies of the neurons. These networks surround the digestive tube from the esophagus

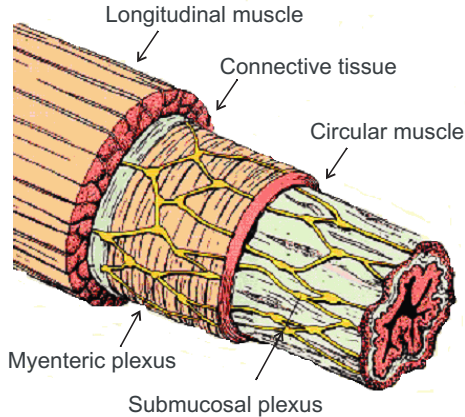


Fig. 1.3 The location of the myenteric and submucosal plexuses of the enteric nervous system in relation to the outer longitudinal and inner circular smooth muscle layers of the gut wall.

to the rectum. There are three morphologically distinct species of neuron, but histochemically a much greater variety when they are characterized by their neuropeptide content. The functional groups of neurons are afferent (sensory), efferent (motor), and interneurons that have synaptic connections with other plexus neurons.

The myenteric plexus regulates the motor activity of the smooth muscle, and in particular, the circular smooth muscle. This property has been the subject of much study, and the outcomes of such studies form the substrate for the chapters that follow in this book. Action potentials in neuron cell bodies are transients, as are the action potentials of smooth muscle fibers. Also, it has been possible for electrophysiologists to record directly from neuronal cell bodies in isolated *ex vivo* preparations of gut because, in some species but particularly the guinea pig, the longitudinal muscle can be easily stripped away to reveal the myenteric plexus.

The function of the submucosal plexus is more uncertain. It is likely that it is involved in the regulation of mucosal transport, mucosal blood flow, and also the immune system of the mucosa, but it is difficult to detect transient changes in these functions that mirror neuronal activity. Moreover, the submucosal plexus cannot be accessed for study in the same way as the myenteric plexus.

The gut may be visualized as consisting of segments that are millimeters in length, each invested with the neuronal circuitry for regulating function and for sensing physicochemical and spatial changes in the gut lumen. Each of these functional units is connected, through interneurons, with the adjacent rostral and caudal functional units. The neuronal architecture of the plexuses mirrors the architecture of the cerebral cortex, while the range of neuropeptide species in enteric neurons is almost identical with those in the brain. Collectively, the intrinsic plexuses of the gut constitute the enteric nervous system (ENS). Nearly a century ago, Langley postulated that the plexi form the third division of the autonomic nervous system, alongside the sympathetic and parasympathetic divisions. This concept was refined by later workers, so that the enteric plexuses were then seen as the “final motor neurons” of the gut, categorized as cholinergic parasympathetic or adrenergic sympathetic neurons utilizing acetylcholine (ACh) and noradrenalin (NA), respectively, as neurotransmitters. Fifty years ago, a population of enteric neurones were identified as “non-cholinergic non-adrenergic” (NANC). The quest to find “the NANC neurotransmitter” segued into the explosion of information on regulatory peptides as neurotransmitters and neuromodulators, leading to the diverse neuronal types now recognized. In recent years, the enteric nervous system has been characterized as the “little brain in the gut,” whereas the sympathetic and parasympathetic divisions serve only as the pathways for communication between the ENS and the central nervous system. Unlike the autonomic nervous system, the ENS neural networks have the property of initiating and performing complex motor programs in response to changing sensory input. The difference between the CNS and the ENS is that the “big brain” — the cerebral cortex — is remote from the tissues that it controls and the sensory input that determines its operation, whereas the “little brain” is a cellular bilayer that is separated by only millimeters from sensory input and motor output.

There is one other important difference between the CNS and ENS. The cerebral cortex is organized with different areas devoted to different functions. In contrast, there are no specialized areas in the ENS, and no need for such differentiation, since every part of the digestive tube contains the neural circuitry that enables the underlying tissues to carry out their functional role.

term “electrical slow wave” is now generally used. The smooth muscle layers of the stomach, small intestine, and colon are electrically isolated, and these organs have differing electrical slow wave frequencies. The “pacemakers” are not discrete structures; they are the regions of the viscus with the fastest intrinsic slow wave frequency. In the stomach and small intestine, the pace-making sites are at the oral end of the organs, in the proximal gastric corpus and just distal to the pylorus respectively, so that the slow waves always propagate in a caudad direction. If the bowel is transacted and the cut ends then rejoined, a permanent stepwise change in frequency will occur at the site of the junction as the continuity of the smooth muscle layers is interrupted by fibrous scar tissue. In such a situation, there will be a new pacemaking site for the bowel distal to the site of the section, at a lower frequency than before.

The situation in the colon is less certain; slow wave activity has been detected but the electrical activity of colonic smooth muscle is complex and remains to be fully characterized. Different layers of the colonic wall may have different slow wave frequencies, and pacemaking sites have not been identified. Understanding the motor physiology of the stomach and small bowel has been possible because of the close similarity in morphology, electrophysiology, and function between man and other mammalian species, but this not the case for the colon.

The electrical activity of the stomach and small bowel can be clearly recorded by electromyography using electrodes attached to the serosal surface of the organs. Such recordings reveal the succession of slow waves, and the associated spike bursts. Slow waves, which reflect the synchronous depolarization of contiguous smooth muscle cells, mark the points in time when contractions of the myocytes are possible. The spike bursts are the summated action potentials of cells in the vicinity of the recording electrode. The correlation between spike bursts and contractile activity can be confirmed by simultaneous recording of pressure changes at the same location.

The electrical slow wave activity of the stomach can also be recorded using electrodes on the surface of the abdomen because the relatively stable position of the stomach within the abdominal cavity provides a consistent electrical vector; this non-invasive technique is known as electrogastrography. The technique is of limited value because spike bursts associated with the gastric slow wave cannot be detected using this method.

The presence, rhythmicity, and propagation of the slow wave in the gut wall are linked to, and may be dependent upon, another tissue element of the gut wall. These are the interstitial cells of Cajal (ICC), first described by Ramón Y Cajal as simple interstitial cells. They are not neuronal elements, but they have the property of excitability. The density of the population of ICC is greatest where slow wave activity is dominant, particularly the small intestine. They are, however, absent, as is slow wave activity, in the esophagus.

It will have occurred to the informed reader that there are close affinities between gastrointestinal smooth muscle and myocardium, albeit that the intrinsic electrical frequency of gut muscle is much slower than in the heart. There is, however, one major difference. Every propagated slow wave in the myocardium induces action potentials resulting in contraction. This is not the case in the gut; the passage of each slow wave provides the opportunity for a contractile event, but whether or not a contraction occurs is determined by the intrinsic innervation. This allows the creation of patterns of motor activity that reflect the need, at any locus, for gut content to be arrested, perturbed, or propelled, and confers great flexibility on the system.

There is one further difference between the smooth muscle of the heart and the gut. The only possible variation in myocardial performance is a change in pacemaking frequency, so as to increase or decrease the heart rate and hence cardiac output. In the gut, pacing frequency does not change, and the motor activity at any point is varied by the presence or absence of action potentials during the passage of the wave of depolarization.

1.5 EXTRINSIC INNERVATION

The co-ordinated motor response to a meal involves the entire gut. Local motor activity is determined by the intrinsic innervation of the gut; since this is continuous from one end of the digestive tract to the other, it might be thought that the transmission of information along the ENS is sufficient for co-ordination. Certainly it suffices for the propagation of peristalsis; distension of a gut segment by a solid bolus stimulates circular muscle contraction above the bolus, and relaxation below, and so the bolus is moved to the next segment. But there are also responses by segments to events that are occurring in a distant segment. One example is the “gastro-colonic response” in which distension of the stomach by a meal provokes the movement of stool

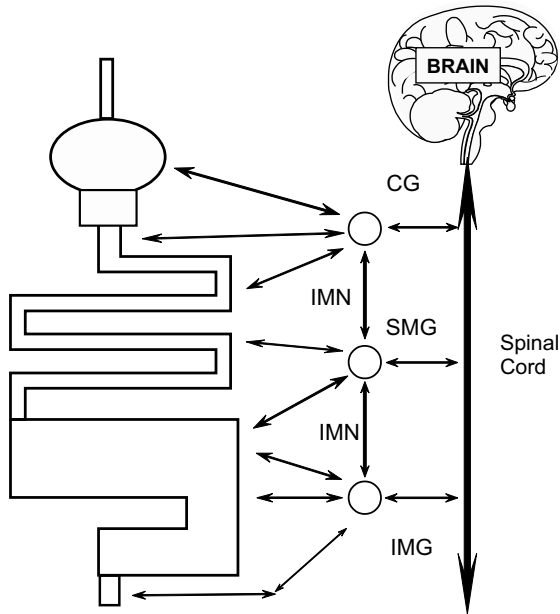


Fig. 1.5 Anatomical connections of the enteric nervous system, prevertebral ganglia, and spinal cord. (CMG = celiac ganglion, SMG = superior mesenteric ganglion, IMG = inferior mesenteric ganglion, IMN = intermesenteric nerve).

from the distal colon into the rectum, provoking the urge to defecate. In contrast, painless distension of the rectum following the ingestion of a meal will diminish the vigor of propulsive activity in the proximal small bowel. Communication between stomach and distal colon along the ENS would involve many synapses.

There is, however, a system for the rapid transmission of information between distant parts of the gut. There are three prevertebral ganglia — celiac, superior mesenteric, and inferior mesenteric — that are connected to the ENS (Fig. 1.5). These ganglia are connected by two intermesenteric nerves. A stimulus in one part of the bowel can travel by an afferent axon to one of the ganglia, along an intermesenteric nerve to the next ganglion, and thence back to the ENS in the axon of an efferent nerve; only three synaptic connections are required. These pathways are essential for the patterns of motor activity that involve the whole of the stomach and small intestine.

Finally, the neural connections between the gut and the brain deserve mention. It has long been known that the vagus nerve, the Xth cranial nerve, innervates the fore-gut as well as the heart. Pavlov's discovery of the conditioned reflex at the end of the 19th century led to the belief that the CNS "controls" the gut. It is now known that the autonomic pathways to the gut are largely afferent, conveying information from sensory receptors in the gut to the brain. These pathways are the parasympathetic vagus and pelvic nerves, and the adrenergic spinal nerves, projecting from the prevertebral ganglia into the spinal cord. Gut-brain interaction has been the subject of serious study for the last three decades, but it would be inappropriate to deal at length with this subject in a book devoted to enteric neurobiology. Suffice it to say that the brain is kept fully informed of events in the digestive tract, even though little, if any, of this information is normally projected into consciousness.

1.6 THE EFFECT OF FOOD ON THE GUT

The effect of food on gut function is not only a profound secretory response, but also a profound motor response. To understand this motor response, it is necessary to consider the activity of the gut in the absence of food — the fasting motor pattern. Recording of contractile events in the fasting gut reveals a stereotypic motor pattern throughout the stomach and small bowel that is repeated, on average, every 90 minutes. First, there is a phase (Phase 1) of motor quiescence, which dominates the greater part of the cycle (Fig. 1.6a). This is followed by a phase (Phase 2) of intermittent contractions. The final part of the cycle (Phase 3) consists of a relatively brief phase of powerful regular contractions, occurring at the frequency of the slow wave at that location: $\nu = 0.05$ Hz in the human stomach, and $\nu = 0.15$ – 0.2 Hz in the duodenum. This cycle is periodic motor activity, the period being the interval between two similar phases, for example between one Phase 3 and the next Phase 3. The effect of food is the abolition of this cyclical motor complex, with its replacement by intermittent contractile activity similar to Phase 2.

The cardinal element of the fasting motor complex is its migratory nature and it is now known as the migrating motor complex (MMC) (Fig. 1.6b). Recording at multiple sites in the stomach and small bowel shows a slow but steady progression of each MMC along the bowel. MMC's may start in

(a) **Periodic motor activity**



Fasting motor activity

- Phase 1 (15-65 min) Motor quiescence
- Phase 2 (65-15 min) Irregular contractions
- Phase 3 (3-8 min) Regular contractions

Postprandial (“fed”) pattern

- resembles Phase 2

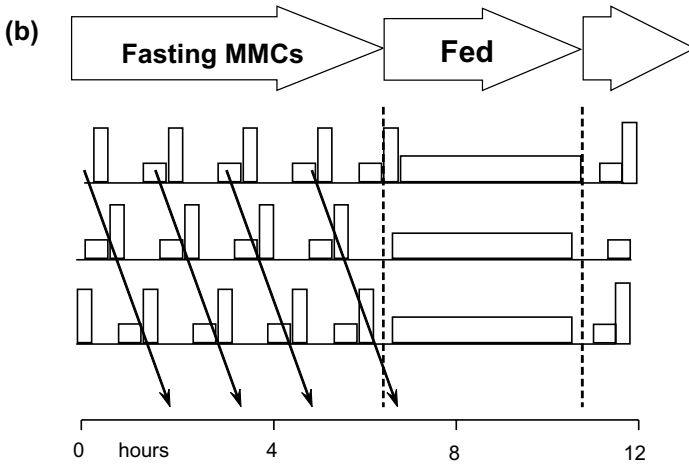


Fig. 1.6 (a) Periodic motor activity of the stomach and small intestine (the upper panel) and data for the approximate duration of the phases of the motor complex (the lower panel). (b) Migrating motor complexes as they are recorded, and of the simultaneous arrest of MMCs on feeding at all levels of the small intestine. The icons for Phases 1–3 of the MMC are defined in Fig. 1.6a.

the stomach, but others are generated in the duodenum. Most MMC’s reach the terminal ileum, but some appear to fade at a more proximal locus. The migration velocity of the MMC is usually measured in centimeters/minute, whereas slow wave — and hence peristalsis — propagation is measured in

centimeters/second. Transit of an MMC from the stomach to the terminal ileum takes 1–2 hours.

The MMC represents a biorhythm which is common to all mammalian species. In man, the periodicity of the MMC is similar to the periodicity of the nREM/REM sleep cycle, but this is not the case in other species, and there is no synchrony between the two biorhythms in man. In man and other carnivorous species, the effect of ingesting a meal is dramatic; the fasting pattern of MMC's is abolished at all levels of the gut almost simultaneously (Fig. 1.6b). The periodic fasting pattern is replaced by a pattern of intermittent contractions, similar to the Phase 2 component of the MMC. This conversion is clearly not due to the local presence of nutrients, as MMC activity on feeding is abolished in the distal small bowel well before the arrival of any nutrient. MMC activity returns only when the last remnants of the meal pass out of the stomach into the duodenum. Clearly, the trigger for the conversion to the fed motor pattern is the detection of nutrients by mucosal chemoreceptors in the proximal duodenum. But these receptors are not connected to the ENS, but are vagal sensory receptors. The arrival of food stimulates vagal afferent input to the dorsal vagal nucleus (Fig. 1.7). In turn, the efferent vagus is activated, and it is the efferent vagal input into the ENS that effects the conversion. The conversion from fasting to fed activity can be abolished experimentally by section of the vagus nerves, and it is impaired in patients who have had truncal vagotomy.

The significance of periodic activity and its abolition by food in terms of enteric neurobiology is that it is now clear that these are motor programs that reside within the enteric nervous system. There are parallels with the central nervous system in that the MMC program like the CNS programs for coordinated locomotor activity, is not expressed at birth. In human newborns, MMC's start to appear 3–6 months after birth. The functional importance of these motor patterns in man is twofold. First, the MMC pattern is required for the propulsion of non-digestible solids that are not broken down to a small particle size in the stomach. During the gastric emptying of a meal, gastric contractions are not powerful, and only particles less than 5 millimeters in diameter are expelled through the pylorus. It is not until the more powerful contractions of the gastric MMC return, and all nutrients have been emptied, that larger non-digestible solids will be expelled from the stomach. Secondly, MMC's play an important role in preventing bacterial overgrowth of the small

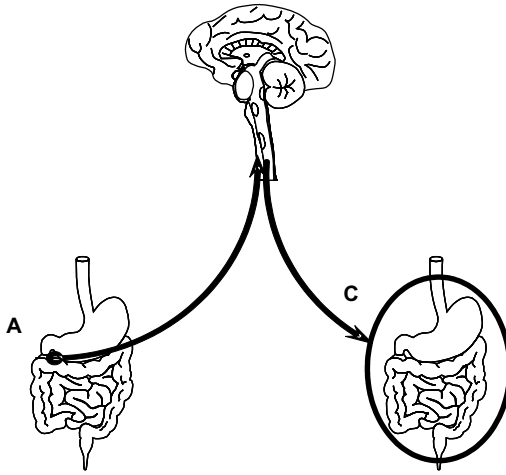


Fig. 1.7 The pathways for the switch between fasting and fed motor activity. The arrival of nutrient in the duodenum (A) is detected by vagal afferents, and transmitted to the dorsal vagal nucleus (B). This activates vagal efferent input to the enteric nervous system (C) that operates the change in motor program from periodic fasting activity to the postprandial pattern.

intestine. Although the ileocecal valve is a barrier to the reflux of bacterial flora from the colon, it is an imperfect barrier. The repetitive scouring action of MMC's in sweeping all intestinal content into the colon is essential to the maintenance of a germ-free lumen in the small bowel. Professor C. Code described the MMC as “the intestinal housekeeper”; research since then has confirmed his prediction.

Finally, some other salient points about periodic and postprandial motor activity:

- i) The genesis of an MMC in the duodenum is accompanied by the release of motilin, a peptide unique to the gut, from mucosal endocrine cells into the bloodstream. Whether this is the cause or the effect of the motor phenomenon remains unresolved.
- ii) Proof that the motor programs reside within the ENS is provided by evidence that the motor programs are damaged or absent in diseases in which the ENS is damaged. This fact allows diagnosticians to use manometric recordings of small bowel motor activity to test the integrity of the ENS in suspected motor disorders of the gut.

- iii) As stated above, when the bowel is transected and rejoined, there is a permanent change in slow wave frequency above and below the site of section. MMC migration is similarly interrupted, but after a few weeks, MMC's cross the site of section and co-ordination is restored. This suggests that, while the continuity of the smooth muscle mass is permanently interrupted by scar tissue, neurons can grow across the gap to restore the integrity of the ENS.
- iv) Mechanoreceptors on the peritoneal surface of the gut respond to pressure — when, for example, the bowel is manhandled by a surgeon during a laparotomy — by inducing a reflex adrenergic blockade of all mechanical activity in the bowel wall. This is a state known as paralytic ileus, and it persists for hours after the stimulus has been removed.

1.7 CLINICAL PHARMACOLOGY

The history of the use of medications intended to modify the motor activity of the gut falls into two distinct phases, namely before and after the identification of the neurotransmitters of the ENS, and the characterization of their many receptors.

The first phase was the use of herbal extracts for the treatment of gastrointestinal ailments. The two commonly used herbal remedies were opium, extracted from the seeds of the poppy *Papaverum Somniferum*, and belladonna, extracted from the berries of *Atropa belladonna*. Opiates have long been used for the treatment of diarrhea, but also for the relief of pain and abdominal discomfort. Their significance in the present context is that opioids are neurotransmitters within the ENS, and the antidiarrheal actions of opiates depend, at least in part, on the diminution of the velocity of transit of bowel content. Belladonna extracts contain atropine alkaloids, which are strongly anticholinergic. Belladonna extracts diminish the propulsive force of the gut, and also the secretion of gastric acid, but their use, although widespread in antiquity, was limited by unwanted adverse effects on other body systems.

The modern era of gut motor pharmacology began with the discovery of two drugs in the 1960s. One drug was *Diphenoxylate (Lomotil)*, an opiate agonist that acts only on opiate receptors in the gut, and thus lacks the unwanted addictive effects of opiates on the central nervous system. It has

proved to be an unrivalled preparation for the management of diarrhea, but its efficacy derives from its effect on absorption rather than propulsion, and it has been largely replaced by *Loperamide* (*Imodium*), which proved to be more effective. The other drug was *Metoclopramide* (*Maxolon*, *Pim-peran*), a substituted benzamide. It was found to have potent anti-emetic properties, but also to accelerate gastric emptying, and from this stemmed the concept of “pro-kinetic” drugs. As receptors in the gut became identified, it became clear that *Metoclopramide* acts both on the dopamine D₂ receptor, and on 5-hydroxytryptamine receptors, where it is a mixed (5-HT₄) agonist and (5-HT₃) antagonist. As pharmaceutical medicine moved from the age of accidental drug discovery to the new era of designer drugs, the search began for “pro-kinetic” drugs that act selectively on gut receptors. One of the drawbacks of the drug was its actions on the central nervous system; indeed, its anti-emetic potency derives from its action on the chemoreceptor trigger zone that initiates emesis.

The aim was to find drugs with a “pro-kinetic” effect on the gut, preferably acting on a single receptor, and free of CNS side-effects because of an inability, in therapeutic dosage, to cross the blood-brain permeability barrier. The first apparent success was *Cisapride* (*Prepulsid*, *Propulsid*), discovered at Janssen Pharmaceutica, Belgium. *Cisapride* is a parasympathomimetic that acts as a strong 5-HT₃- and weak 5-HT₄-receptor agonist. Stimulation of the serotonin receptors increases acetylcholine release in the ENS. *Cisapride* did indeed prove useful in the treatment of gastro-oesophageal reflux, by increasing the force of peristalsis and so increasing the clearance of acid refluxed from the stomach. But other claimed benefits were inconsistent, and the drug was withdrawn by the Food and Drug Administration (USA) in 2000 because of adverse cardiac side effects. Two other drugs acting on serotonin receptors in the gut are *Tegaserod* (*Zelnorm*), a 5-HT₄ agonist, and *Alosetron* (*Lotronex*), a 5-HT₃ agonist. Both have been promoted for different components of the irritable bowel syndrome, but their success has not been overwhelming.

While the drugs mentioned simulated metoclopramide in their actions on the gut serotonin axis — but without any central effects — another drug, *Domperidone*, was intended as a dopamine D₂ antagonist to have some of the properties of *Metoclopramide*. But its potency is limited, and it also stimulates the release of prolactin from the hypothalamus.

Two more pharmacological approaches deserve mention. *Trimebutine* is a gut-selective opioid agonist developed in France aimed at relieving various gastrointestinal discomforts. It was never submitted for licensing in the USA or the UK, but is widely used in Europe, Asia, and South America. However, such success as it has had owes more to successful marketing than proven efficacy. Secondly, there are the derivatives of erythromycin, a macrolide antibiotic. Erythromycin was known to be associated with gastrointestinal side-effects, and when the effect of the drug on gut motor activity was studied, it emerged that it mimics the effects of motilin. Manipulation of the molecular structure by substitution of the sugars in the macrolide produced molecules that preserved the motilin effect while making it devoid of any antibacterial action. An ideal candidate disease for such a drug is the gastroparesis (paralysis of gastric motor activity) that occurs in Type 1 diabetes mellitus, and this proved to be the case. Sadly, this relatively unusual condition did not seem to justify the cost of bringing the drug to the market.

What all of these drugs share is dubious therapeutic efficacy. They have been designed to alleviate the spectrum of so-called “Functional Gastrointestinal Disorders” (FGID’s), which include such ill-defined entities as irritable bowel syndrome and non-ulcer dyspepsia. In these disorders, controlled randomized blinded trials show a high level of placebo response at about 30%, however, measured. Drugs such as *Tegaserod* and *Alosetron* show an improvement in 50% of subjects, but that is only an improvement of 20% over placebo. The reason for this is almost certainly that the indications for their use are vague, both in terms of diagnostic precision and pathophysiology. Pharmacological sophistication may have outstripped our understanding of the biology of these disorders. On the other hand, perhaps the best is yet to come. The chapters that follow describe methodologies that should lead to the development of other drugs, and at considerably lower cost than is the case today.