Physiol. Res. 52: 1-30, 2003

MINIREVIEW

Neurohumoral Control of Gastrointestinal Motility

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Received December 6, 2001
Accepted April 25, 2002

Summary

Neurohumoral substances and their receptors play a major part in the complex regulation of gastrointestinal motility and have therefore been the predominant targets for drug development. The numerous receptors involved in motility are located mainly on smooth muscle cells and neuronal structures in the extrinsic and intrinsic parts of the enteric nervous system. Within this system, receptor agonists and antagonists interacts directly to modify excitatory or inhibitory signals. In view of this complexity it is not surprising that our knowledge about the mechanisms of actions of the various neurohormones and drugs affecting gut motility has been rather fragmented and incomplete. However, recently substantial progress has been achieved, and drug therapy for gut dysmotility is emerging, based primarily on neurohumoral receptors. This paper presents a selective review of the neurohumoral regulatory mechanisms of gastrointestinal motility. In this context, the physiology and pharmacology of the smooth muscle cells, gastrointestinal motility and dysmotility, the enteric nervous system, gastrointestinal reflexes, and serotonin is presented. Further investigation and understanding of the transmitters and receptors involved in especially the reflex activation of peristalsis is crucial for the development of novel therapies for motility disorders.

Key words

5-Hydroxytryptamine • Enteric Nervous System • Gastrointestinal • Hormones • Interstitial Cells of Cajal • Motility • Review • Serotonin

1. Introduction

Gastrointestinal (GI) motility is an integrated process including myoelectrical activity, contractile activity, tone, compliance and transit. These different entities of motility can be generated and modulated by local and circulating neurohumoral substances. The importance of neurohumoral control of motility goes back to 1859, where C. Bernhard observed profuse diarrhea (”paralytic secretion”) and vigorous intestinal motility (”hunger contractions”) after external sympathetic denervation of the dog gut. Brunton and Pye-Smith attributed correctly this phenomenon to a disruption of neural pathways within the intestinal wall. Later, the term peristalsis was introduced (Modlin *et al.* 2000). During the last decade substantial new knowledge has been accomplished on especially the involvement of the enteric nervous system (ENS) in these processes.

The purpose of this review is to present an overview and some new interesting findings on the mechanism by which GI motility is controlled and

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modulated by neurohumoral substances with focus on the small intestine and serotonin (5-hydrotryptamine, 5-HT).

2. The smooth muscle of the gut

Structure

Smooth muscle cells of the gut behave as unitary types and consists of a thin outer longitudinal layer and a thick, densely innervated circular layer. The thickness of the two layers varies both between species and regions (Olsson and Holmgren 2001). The layers are separated by laminar septae into bundles about 1 mm long, which act as contractile units. The muscle cells are embedded in a connective tissue matrix, a product of their synthetic and secretory activity consisting mainly of elastic and collagen fibrils. These layers include glial cells, fibroblasts, and a distinctive population of cells, the interstitial cells of Cajal. The muscle cell plasma membranes consist of two specialized structures known as caveolae and dense bands. The caveolae are basket-shaped and represents calcium stores. Clusters of caveolae are separated form each other by dense bands that occupy about one-half of the surface of the cell. The dense bands are points of attachment of thin actin filaments. Intermediate filaments link dense bands in the membrane to dense bodies in the cytoplasm and transmit the force generated by the contractile apparatus within the cell to the entire surface of the cell. Gap junctions are abundant in circular and rare in longitudinal muscle layer, and they permit movement of intracellular regulatory molecules, all suggesting a significant functional role (Makhlouf 1995, Horowitz *et al.* 1996, Murphy 1998, Daniel *et al.* 2001).

Contractile filaments

Three types of filaments exist: thin actin, thick myosin and intermediate desmin filaments. These filaments interdigite with each other. Following electric or mechanical coupling, the essential first step in smooth muscle contraction is generated: phosphorylation by myosin light chain kinase. Several steps lead to the activation of the enzyme. Cytoplasmic calcium sequentially binds to the regulatory protein, calmodulin, which eventually greatly enhances the ability of actin to activate myosin Mg^{2+}-ATPase and bring about the hydrolysis of adenosine triphosphate (ATP) bound to the myosin head. The interaction of myosin and actin with hydrolysis of ATP occurs in a cycle, the essential feature of which is a shift in the affinity of myosin for actin (Makhlouf 1995, Horowitz *et al.* 1996, Murphy 1998).

The signal transduction pathway

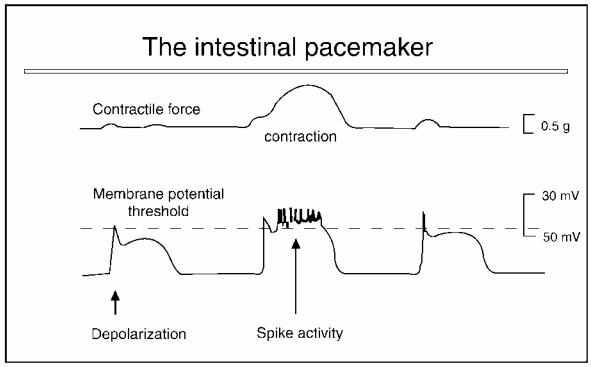
In smooth muscle undergoing contraction or relaxation, agonists act mainly by means of intracellular messengers to induce the release or stimulate the sequestration of calcium (Ca^{2+}). The signal transduction pathway of an external neurohumoral signal into an internal signal is a process that involves sequential activation of at least three membrane proteins: a receptor, a guanosine triphosphate (GTP)-binding protein, and phospholipase C (PLC), which is capable of mobilizing intracellular Ca^{2+}. Production of cyclic adenosine monophosphate (cAMP, e.g. by β-adrenergic agonists), cyclic guanylate monophosphate (cGMP, e.g. by nitric oxide, NO) or both (e.g. by vasoactive intestinal polypeptide, VIP), leads to activation of protein kinase A and C, respectively. These kinases cause a decrease in cytosolic Ca^{2+} and in the sensitivity of contractile proteins to Ca^{2+}. PLC hydrolyses inositol phospholipids located in the plasma membrane, generating several metabolites, one being 1,4,5-trisphosphate (IP_3) and another being diacylglycerol (DG). One metabolic product of IP_3, IP_4, regulates Ca^{2+} influx into the cell and its reuptake into the intracellular store. Accordingly, the exposure of smooth muscle cells derived from the circular muscle layer to a contractile agonist induces rapid contraction accompanied by an increase in IP_3, cytosolic Ca^{2+}, and net Ca^{2+} influx. The peak responses of IP_3, cytosolic Ca^{2+}, Ca^{2+} efflux and contraction are concentration dependent and closely correlated with each other. The mechanism in isolated cells of the longitudinal muscle layer is markedly different from those of the circular layer and less sensitive. IP_3 participate little or not at all in longitudinal muscle cells, while DG seems involved instead (Murphy 1998).

Electrical properties

The resting membrane potential of muscle cells of the gut is in the range of –40 to –80 mV and is largely determined by activity of the Na^+-K^+ pump and K^+ channels. In addition to passive ion-selective channels, the plasma membrane contains ion-selective channels that can be regulated by membrane potential and by various neurohumoral agents. Especially, voltage-gated Ca^{2+} and several types of K^+ channels have been identified. High conductance channels with mixed selectivity for K^+ and Na^+ carry an inward depolarizing current and are

activated at membrane potentials negative to –70 mV, known as the pacemaker potential (Fig. 1). Ca^{2+} channels and Ca^{2+} activated K^+ channels constitute the electrical apparatus that sustains rhythmicity in the smooth muscle. The cycle speed, amplitude and duration depends on the relative proportions of active Ca^{2+} and K^+ channels, modulated by neurohumoral agents, participation of other voltage-gated or ligand-gated channels, and coupling of muscle cells to each other and to pacemaker cells (Murphy 1998, Makhlouf 1995).

Fig. 1. *Smooth muscle contraction in the small intestine. Contraction occurs when spike activity superimposes on the slow wave and depolarization reaches a critical threshold.*



Slow waves and the interstitial cells of Cajal

The basic electrical rhythms in the gut are fairly constant and characterized by slow waves. However, smooth muscle cells lack the ionic mechanisms necessary to regenerate electrical slow waves. A typical slow wave consists of the following sequence: rapid depolarization (upstroke), partial depolarization, a sustained plateau, and complete repolarization to the resting membrane potential (Fig. 1). In most cases when threshold is reached, spike potentials occur and are superimposed on the slow waves plateau phase. Spike potentials are membrane depolarizations that are much shorter than the slow wave, usually only 10 to 100 ms long, with amplitudes of up to 50 mV. The ionic determinant of the spike potential appears to be membrane Ca^{2+} flux. Excitatory agonists, such as acetylcholine (ACh), stimulate intestinal phasic motor activity by enhancing spike potential activity, resulting in a contractile wave passing down the gut (Makhlouf 1995, Murphy 1998).

The slow waves oscillate at different frequencies, amplitudes, and durations in different regions of the gut. The frequency is 3 cycles/min in the antrum of the stomach, 12 cycles/min in the duodenum, 8 cycles/min in the ileum and 6-10 cycles/min in the colon of man. The precise mechanisms that trigger and set the pace of slow waves is unknown and only a few stimuli and agents are known to affect the slow wave frequency and spike activity. Among these are a few neurohumoral inputs, that influences the amplitude of plateau potential, the frequency of spike potential and determines the magnitude and occurrence of slow waves and phasic contractions in the intestinal cells (Makhlouf 1995, Murphy 1998).

The search for the origin of rhythmicity in intestinal contraction has identified pacemaker regions of the slow waves located at the myenteric and submucous borders of circular muscles and contains a network of cells known as the interstitial cells of Cajal (ICC). These ICC cells are distinctive populations of muscle-like, stellate cells with large nuclei and an abundance of surface caveolae, mitochondriae and rough endoplasmic reticulum. The distribution of ICC cells depends on the species, age and the region of GI tract, but can be found in both the circular and longitudinal muscle layers from the esophagus to the anus. ICC cells can be detected as early as 14 weeks of gestation in the upper part of the small intestine, 23 weeks of gestation in the colon and after 34 weeks of gestation in the rectum (Murphy 1998, Huizinga 1999, Rumessen and Thuneberg 1996, Huizinga *et al.* 2000, Hanani and Freund 2000).

ICC cells are equivalent to the Purkinje fibers of the heart. They make contact with each other and with muscle cells and nerve terminals and functions as the pacemakers in GI muscles by initiating rhythmic electrical activity (Vanderwinden 1999). Different classes of ICCs exist and they express specific ionic conductance and c-kit, which is a trans cell membrane tyrosine kinase receptor (Sanders *et al.* 1999). By regulating ionic conductances in ICCs, neurohumoral substances can influence the resting potentials and excitability of coupled smooth muscle cells and thereby the motility (Ward *et al.* 2000). As such, NO generates slow electrical oscillations in cells near the myenteric edge of the circular muscle layer, which resemble slow waves generated by ICCs (Keef *et al.* 2002). ICCs have receptors both for the inhibitory transmitter NO and for excitatory tachykinin transmitters (Kunze and Furness 1999), muscarinic and VIP receptors (Camilleri 2001a).

The consequence of loss or defects in ICC cells is abnormal gut motility: gastric distension, abnormal small bowel motility, prominent ileus, inflammatory

bowel disease, chronic idiopathic intestinal pseudo-obstruction (CIP), GI stromal tumors and multiple GI autonomic tumors, achalasia, intestinal obstruction with hypertrophy in the small intestine, Hirschsprung's disease, juvenile and adult intestinal pseudoobstruction, slow transit constipation, anorectal malformations, post-infectious and Chagas disease (He *et al.* 2000, Sanders *et al.* 1999, Hagger *et al.* 2000, Takayama *et al.* 2000, Camilleri 2001a, Porcher *et al.* 2002).

Smooth muscle contraction

The smooth muscle of the gut exhibits two distinct types of contractions: tonic and rhythmic phasic contractions to cause mixing and propulsive movements (i.e. segmentation). The motility function of each type of contraction and the neurohumoral, electric, and cellular mechanisms that regulate them, are very different. The fact that the small intestine becomes dilated in CIP and during the administration of glucagon, indicates that some level of basal tone exists under normal fasting conditions and following biomechanical stimulation. Two kinds of tone exist in the gut: neurogenic and myogenic. The neurogenic tone results from a constant low discharge of excitatory innervation, while the myogenic tone results from a property of the muscle itself (Gregersen *et al.* 1992, Gregersen and Christensen 2000). The rhythmic phasic contractions produce mixing and slow distal propulsion of luminal content in the fasting and the postprandial states. The maximal frequency and direction of propagation of these contractions are regulated by slow waves. Release of neurotransmitters from the motorneurons determines whether the smooth muscle will contract, increase tone or not. In the presence of excitatory neurotransmitters, muscle cell membrane receptors are activated to produce excitatory junction potentials and subsequently increase smooth muscle contraction, and visa versa. The response to physiological excitatory stimuli such as bradykinin, ACh and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) are characterized by an increase in sensitivity to agonists with a more tonic nature of motility (Sanders *et al.* 1999). The distance of propagation of individual phasic contractions depends on the length of the segment over which the excitatory neurotransmitter is released concurrently, and the distance over which the slow waves are synchronized. Phasic contractions also occur as groups, generating the migrating motor complex (MMC) and migrating clustered contractions (Sarna *et al.* 2000, Hansen 2002).

Age and gender

Women and elderly persons have impaired esophageal motor function, gastric emptying and colonic transit as compared to males and younger healthy adults, respectively. Plasma levels of oestrogen and progesterone does not seem be of importance, as the stage of the menstrual cycle does not affect gastric or jejunal myoelectric activity (Madsen 1992, Gianaros *et al.* 2001). It is likely, but uncertain, that the gender and aging is also of importance for small intestinal motility. For example one manometric study showed that the postprandial motility did not display gender difference in any parameter examined and that the majority of patterns of motility are similar in menstruating women and men, whereas certain aspects of the MMC, most conspicuously propagation velocity and phase III contraction amplitude, differ. The circadian variation of phase III contraction frequency is present in both women and men (Aytug *et al.* 2001). Another study showed more frequent cluster contractions and slower migration of the MMC in older subjects during fasting and postprandially (Husebye and Engedal 1992, Hansen 2002). However, the rest of basic patterns of fasting and stimulated motility and transit time are maintained throughout the process of aging and without any gender differences (Husebye and Engedal 1992). In another study, using a different method, women had slower small intestinal transit than men (Sadik *et al.* 2001). These differences could be due to lack of full relationship between myoactivity and transit time studies.

3. Regulation of gut motility

The regulation of smooth muscle activity and gut motility takes place at several levels. Hormones and neurotransmitters are the dominating components, which act and interact directly and indirectly on muscle cells. The use of knockout animals, in which the development or synthesis of particular neurohumoral transmitter substances or receptors has been prevented, has turned out to be a significant novel tool for studying neurohumoral control of gut motility (Spencer 2001).

The hormonal influence and the interplay with the ENS, takes place after and in between meals. The postprandial endocrine response includes release of insulin, neurotensin, cholecystokinin (CCK), gastrin, glucagon-like-peptides (GLP-1 and GLP-2), glucose-dependent insulinotropic polypeptide (GIP, previously known as gastric inhibitory peptide), but not motilin nor somatostatin (Medhus *et al.* 1999). These released hormones have all been demonstrated to have functional

importance for digestion. For example, CCK is released into the circulation from the upper small intestine, causing direct contraction of muscle cells in the gallbladder and neurally mediated relaxation of muscle cells in the sphincter Oddi, which is mediated by VIP at the neuromuscular junction.

There is also hormonal release and subsequent neural activation arising within the lumen from the mechanical and chemical properties of food and digestive secretions. Hormones are released locally from endocrine cells in the mucosal lining (e.g. 5-HT from enterochromaffin cells, EC cells) and modulate motility by activating receptors on sensory fibers, the extrinsic (e.g. vagal) and intrinsic primary afferent neurons (IPANs), and again back on the endocrine cells in an autoregulatory fashion. This system conveys sensory information, so the CNS can evaluate GI activity and modulate motility accordingly (Fig. 2 and 3).

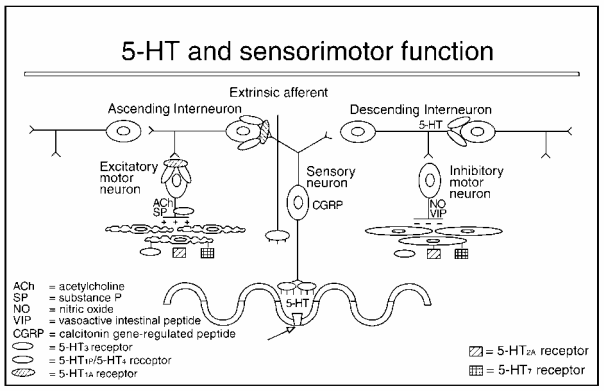


Fig. 2. *5-HT and sensorimotor function. 5-HT is released from mucosal sources. 5-HT induce peristaltic motor activity. Intrinsic and extrinsic neuronal excitatory and inhibitory pathways and several 5-HT receptors are involved in this process. Acetylcholine, substance P, nitric oxide, vasoactive intestinal peptide and calcitonin gene-regulated peptide is involved in the processes. See Fig. 3 for further details.*

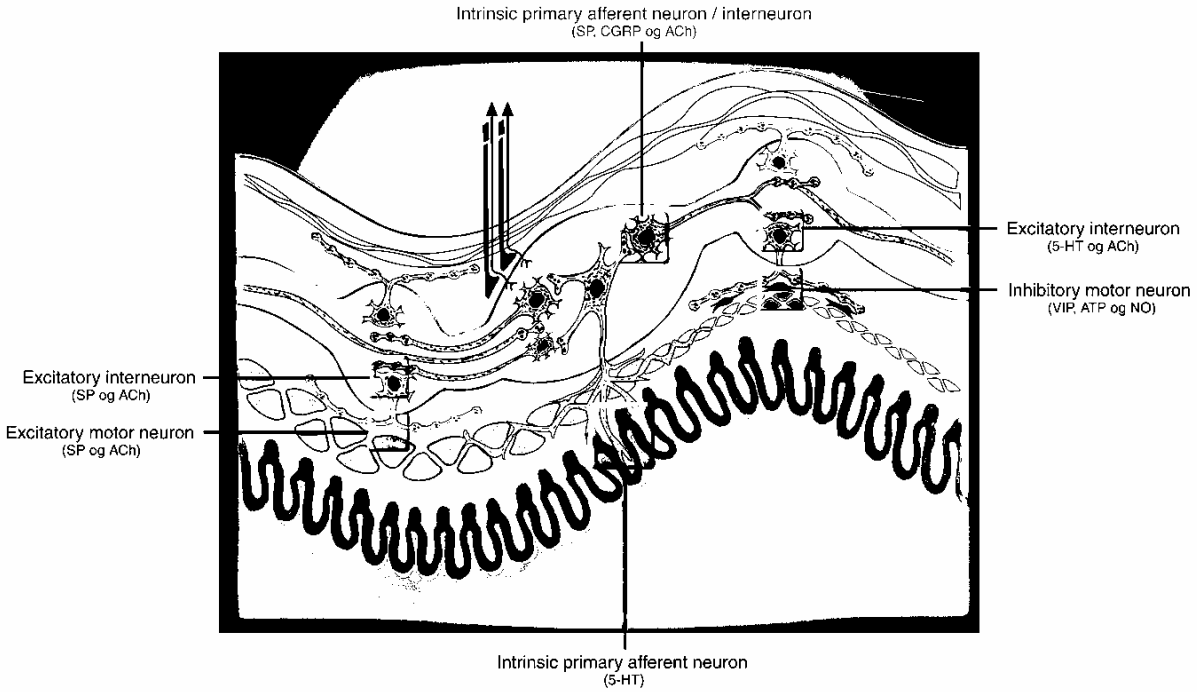


Fig. 3. *The peristaltic reflex in the small intestine. Following mucosal stimulation, 5-HT is released from enterochromaffin cells to intrinsic primary afferent neurons (IPANs with 5-HT$_{1P}$, 5-HT$_3$ and 5-HT$_4$ receptors) and extrinsic vagal and spinal afferents (with 5-HT$_3$ receptors). IPANs release substance (SP) acetylcholine (ACh), glutamate and calcitonin gene-regulated peptide (CGRP) to interneurons. Excitatory interneurons release SP and ACh orally to excitatory motorneurons, while 5-HT and ACh is released aborally to inhibitory motorneurons. Excitatory motorneurons release SP and ACh to muscles, while inhibitory motorneurons release nitric oxide (NO), vasoactive intestinal peptide (VIP) and adenosine triphosphate (ATP) to muscles. Efferent sympathetics release norepinephrine (NE), somatostatin (SOM) and neuropeptide I, while efferent parasympathetics release ACh (not shown).*

The neuronal regulation of GI motility involves intrinsic as well as extrinsic nerves. The intrinsic innervation involves the enteric nervous system (ENS), which consists of ganglionated and non-ganglionated plexi. The extrinsic innervation involves the vagus nerve and splanchnic nerves to the stomach and upper intestine, while the pelvic nerves supply the distal intestines. Extrinsic neurons of the sympathetic and parasympathetic systems influence smooth muscle indirectly by acting on neurons of the myenteric plexus. However also neurons from the submucous plexus innervate the innermost layers of circular muscle, at least in large species. The smooth muscle cells form an electrical syncytium that is innervated by hundreds of excitatory and inhibitory neurons. In general, the control systems for motility are amazingly similar between species. Inhibitory stimuli (relaxing motorneurons) are exerted by VIP, pituitary adenylate cyclase activating polypeptide (PACAP) and NO, while excitatory stimuli (contracting motorneurons) are exerted by tachykinins, ACh and 5-HT. Again other neurotransmitters modulate the release of these transmitters from motorneurons. For example, reflex activation of myenteric neurons by stimuli, such as stretch or mucosal stimulation, causes the release of VIP, NO production, and muscle relaxation (Kunze and Furness 1999, Olsson and Holmgren 2001).

The GI tract is connected to the CNS through the autonomic nervous system (*the brain-gut axis*). The CNS is able to modulate, but not entirely control, the motor activity by sending instructions *via* the two components of the extrinsic autonomic nervous system: the sympathetic and parasympathetic nervous system. As such several peptidergic (e.g. opioids, thyrotropin-releasing hormone - TRH, corticotropin-releasing hormone - CRF, bombesin, calcitonin gene-regulated peptide - CGRP, neurotensin and CCK) and non-peptidergic (e.g. 5-HT, prostaglandins, dopamine and opioids) have been demonstrated to affect motility following stimulation directly of the CNS. For example, pancreatic polypeptide Y (PPY) is released into the circulation from the endocrine cell in the gut and directly influences central neuronal function and thereby gut motility (Rogers *et al.* 1995). The parasympathetic fibers transmit their instructions *via* the release of ACh to speed up motility, while the sympathetic fiber release norepinephrine (NE), somatostatin and neuropeptide Y (NPY) to slow motility. The activity of the autonomic nervous system is influenced by several factors, including stress, emotion and eating. For example, nociception, following distension and inflammation of the gut, is mediated following the release of 5-HT and tachykinins and subsequent activating of neurogenic 5-HT_{1A}, 5-HT_3, 5-HT_4 and neurokinin NK_1, NK_2 and NK_3 receptors. They are activated in a very complex manner, some centrally, some peripheral, some stimulatory, some inhibitory, some in the stomach, some in the intestines, etc. (Gue and Bueno 1996).

In the small intestine, two populations of sensory neurons have been identified. The first, activated by mucosal stimuli, is wholly intrinsic, and the second, activated by muscle stretch (i.e. mechanosensory), has neuronal cell bodies in the dorsal root ganglia. Two types of mechanosensory neurons exist. Vagal afferents mediate physiological messages in low threshold Aδ and C fibers. Spinal afferents on the other hand mediates nociceptive messages in wide range of high threshold Aδ and C fibers. The IPANs in the myenteric ganglia have been identified to be of major importance for the physiological motor response to digestion. They are numerous and make direct contact with motorneurons and interneurons. The mucosa contains cells that facilitate GI function, such as the EC cells. EC cells release 5-HT and are endowed with at least stimulatory 5-HT_3 and inhibitory 5-HT_4 receptors, and maybe also stimulatory 5-HT_1 and 5-HT_2 receptors (Gebauer *et al.* 1993, Schworer and Ramadori 1998). The interneurons receive instructions from the sensory neurons, which forward information from the EC cells, and from postganglionic termini of extrinsic autonomic nerve fibers. The sensory neurons include connections to the mucosa and fibers that run through the circular muscles. Concentrated in the same areas are the ICC cells. The muscle cells in the longitudinal and circular muscle layer are innervated and therefore linked to the myenteric plexus. The longitudinal layer is innervated by excitatory motorneurons, whereas the circular layer is innervated by both inhibitory and excitatory motorneurons. Afferent extrinsic nerve fibers, which travel along the side of the autonomic nerves in the area, carry sensory information from the ENS, *via* the vagus and spinal cord, back to CNS (Kunze and Furness 1999).

Neurons in the myenteric plexus project their fibers to neurons in the same plexus, the submucous plexus and paravertebral ganglia, and to cells in the circular and longitudinal muscle layers. Neurons of the myenteric plexus of the small intestine fall into two broad categories: those that contain VIP with NO synthase, and

those that contain SP with virtually no overlap of the two. VIP neurons also contain homologous peptides, e.g. peptide histidine-methionine. SP neurons also contain homologous peptides, e.g. substance K (SK). It is likely that ACh coexist with SP and SK in most neurons. Subpopulations of neurons within these categories contain one or more of the following: bombesin (i.e. gastrin-releasing peptide), NPY, the opioid peptides, dynorphin and met-enkephalin, and galanin. A subpopulation of neurons contain GABA, 5-HT or somatostatin. Neurons that contain 5-HT or somatostatin project their fibers exclusively within the myenteric plexus and influence smooth muscle cells only directly by means of other neurons. Receptors for most of these agents and others have been identified on smooth muscle cells of the gut. Some neurotransmitters have been identified as of specific importance for contraction and relaxation in a specific region of the gut. For example, NO and CCK seems important for relaxation of the lower esophageal sphincter (LES), the antrum and fundus of the stomach, the pylorus and the duodenum (Kuiken *et al.* 2002), while 5-HT and motilin are important for antroduodenojejunal contractions.

Table 1. Dominating effect of some neurohumoral substances on intestinal contraction in vivo.

Stimulatory	Inhibitory
ACh	CGRP
Adenosine	*GABA*
Bombesin	Galanin
CCK	Glucagon
GRP	NPY
Histamin	Neurotensin
Motilin	NO
Neurokinin A	PACAP
Opioids	PHI
PGE_2	PYY
Serotonin	Secretin
SP	Somatostatin
TRH	VIP

GRP, gastrin releasing polypeptide; NO, nitric oxide; PGE_2, prostaglandin E_2; TRH, thyrotropin-releasing hormone; CGRP, calcitonin gene-regulated peptide; GABA, gamma butyric acid; NPY, neuropeptide Y; PACAP, pituitary adenylate cyclase activating polypeptide; PHI, peptide histidine isoleucine; PYY, peptide YY; VIP, vasoactive intestinal polypeptide.

Changes in the neurohumoral response to stimuli have been demonstrated in certain conditions involving dysmotility. In the carcinoid syndrome, small intestinal and colonic transit is accelerated (der Ohe *et al.* 1993), while in slow transit constipation, there is an increased secretion of proximal gut hormones and reduced secretion of distal gut hormones**.** Abnormal postprandial levels of motilin, CCK, neurotensin and somatostatin (Peracchi *et al.* 1999), and fewer colonic enteroglucagon- and 5-HT-immunoreactive cells are present (El Salhy *et al.* 1999). As such, treatment with neurotrophic factors improves gut motility for patients with constipation, by mainly increasing the sensitivity to excitatory transmitters and reducing the inhibitory innervation (Camilleri 2001a).

In general neurohormones can be divided into those primarily contracting or relaxing (Table 1), and predominantly modulating upper GI motility (CCK, PPY, gastrin, galanin, GLP-1, motilin, neurotensin and secretin) or lower intestinal motility (e.g. peptide YY) or both (e.g. 5-HT).

4. Serotonin

Serotonin (5-HT) is an important neurohumoral transmitter, that is synthesized and stored in several cell types, mainly in EC cells (90 %) and neurons (10 %) of the gut. 5-HT is released into the blood postprandially and in response to changes in pressure across the gut wall, as well as to noxious stimuli (Bearcroft *et al.* 1998). 5-HT is released into the gut wall from the basolateral stores of the EC cells and probably spills over into the lumen (Hansen and Skadhauge 1997). One of the reasons for the strategic location of the EC cell is the close proximity to the mucosal sensory nerve endings, and interganglionic neurons, which synapse on motor excitatory and inhibitory neurons.

Extensive investigations have been performed to determine the role of 5-HT in the physiological and pathological regulation of gut motility. However, the precise roles of 5-HT and 5-HT receptors are not fully understood yet. This is partly because of the large number of 5-HT receptor subtypes and their diverse locations and effects. The affinity of the neuronal receptors is much greater than that of smooth muscle. As a result the effects of administered 5-HT receptor agonists and antagonists are primarily as those resulting from the activation of neuronal receptors (Sarna *et al.* 2000). In the following, an attempt to summarize the current knowledge is presented.

Exogenous intravenous 5-HT increases contraction amplitudes in the gastric antrum, duodenum, jejunum and ileum (Hopkinson *et al.* 1989, Nakajima *et al.* 1997). In the small intestine, 5-HT stimulates circular contractions during phase I of the manometric MMC, induce propagated contractions and more frequent and faster propagating MMC complexes (Ormsbee *et al.* 1984, Siegle *et al.* 1990, Valdovinos *et al.* 1993, Lordal *et al.* 1998, Hansen *et al.* 2000). Not only the circular muscles are stimulated by 5-HT, but also the longitudinal muscles in the human stomach, duodenum and jejunum (Fishlock *et al.* 1965). In the colon, exogenous intravenous 5-HT stimulates motility along the entire length, by inducing phasic contractions, but not giant motor complexes (GMCs) (Boeckxstaens *et al.* 1990, Nagakura *et al.* 1996a, Nagakura *et al.* 1996b). Also exogenous intraluminal 5-HT evokes hypermotility in animals and probably man (Gronstad *et al.* 1987, Ahlman 1992, own unpublished observations). Endogenous 5-HT has been demonstrated to have similar effects as exogenous 5-HT. As such, selective 5-hydroxytryptamine reuptake inhibitors interferes with the stimulated esophageal motor responses (Boeckaert *et al.* 2001), reduce the interdigestive gastric phase III activity (Haga *et al.* 1996), reduce the mean MMC periodicity and increase the propagation velocity of phase III in the small intestine and reduce the orocecal transit time (Gorard *et al.* 1994) in healthy humans. The importance of serotonergic neurotransmission to the motility has also been demonstrated by experiments in which 5,7-dihydroxytryptamine was employed to selectively destroy serotonergic neurons. These experiments established that normal intestinal motility is diminished and transit down the bowel is slowed when serotonergic neurons are lost. The congenital loss of enteric serotonergic neurons, which occurs in mice with mutations in mash-1 gene, is associated with the lethal absence of intestinal motility (Gershon M, personal communication).

Table 2. Effect of 5-HT receptors on gastrointestinal motility. The overall dominating effect of 5-HT receptors is presented.

Receptor / gut segment	Lower esophageal sphincter	Stomach	Small intestine	Large intestine	Rectum
1	↑	↓	↑	↓	↓
2	?	↑	↑	↑	↑
3	↑	↑	↑	↑	?
4	↑	↑	↑	↑↓	↓
7	?	?	↑	↓	↓

↓ - *inhibition of motility or tone,* ↑ - *stimulation of motility or tone,* ? - *unknown effect.*

5-HT receptors

A variety of 5-HT receptors have been identified and the locations and subtypes of these receptors vary among species. Fourteen different 5-HT receptors are classified into seven receptor subtypes. The roles of 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4 and 5-HT_7 receptors have been studied in the gut (Fig. 2, Table 2). A great deal of work has also been done on 5-HT_{1P} receptors, which might be similar or closely related to the 5-HT_4 receptors. For 5-HT receptors located on smooth muscle cells, four types have been demonstrated: 5-HT_{2A}, 5-HT_{2B}, 5-HT_4 and 5-HT_7. Smooth muscle 5-HT receptors contract or relax: 5-HT_{2A} and likely 5-HT_{2B} receptors contract, while 5-HT_4 and 5HT_7 receptors relax. Neuronal 5-HT receptors enhance or inhibit transmitter release and thereby modulate contraction: 5-HT_{1A} inhibits, while 5-HT_3 and 5-HT_4 (5-HT_{1P}) receptors excite. Obviously, 5-HT receptors can therefore act in concert or have opposing effects. For example, 5-HT receptors coexist on smooth muscle cells in the human small intestine, where 5-HT_{2A} receptors mediate contraction, while 5-HT_4 receptors mediate relaxation (Borman and Burleigh 1997). Furthermore, the potencies of 5-HT receptor active agents are species and region-dependent.

An important aspect is the fact that most 5-HT receptors do not seem to affect normal function, but only in disease states. An example for this is 5-HT_3 receptor antagonist, alosetron, which delays colonic transit in diarrhea-predominant (D)-IBS patients, but not in normals (Camilleri *et al.* 1999, De Ponti and Tonini 2001).

5-HT_1 receptor subtype

There is growing evidence for the involvement of 5-HT_1 receptors in the control of gut motility. 5-HT_1 agonism (e.g. by the 5-HT_{1A} agonist, buspirone or the 5-$HT_{1B/D}$ agonist, sumatriptan) alters esophageal motility (Houghton *et al.* 1994) by preventing the natural decay in rate of transient LES relaxations postprandially (Sifrim *et al.* 1999, Foster *et al.* 1999). They also suppress gastric phase III activity (Tack *et al.* 1998), delay gastric emptying by increasing the lag period (Houghton *et al.* 1992, Coulie *et al.* 1997), increase fundic and antral relaxation (Vingerhagen *et al.* 2000), decrease postprandial antral motility (Coulie *et al.* 1997) in healthy volunteers, but induce duodenal phase III activity in patients suffering from abnormal upper GI motility (Mathis *et al.* 2001a). Most of these effects probably increase the occurrence of gastroesophageal reflux. In the small intestine, 5-HT_1 agonism stimulate peristaltic activity (Buchheit and Buhl 1994), induce premature jejunal phase III activity and shortens the cycle length of the MMC on the expense of phase II activity (Coulie *et al.* 1997, Tack *et al.* 1998, Coulie *et al.* 1999, Tack 2000, Tack and Vanden Berghe 2000). Confusing the picture, sumatriptan in a recent study, increased the length of the MMC in both the stomach and duodenum by prolonging phase II, but not phase III (Calvert *et al.* 2001). In summary, the net effect of 5-HT_1 agonism on antroduodenal MMC in man seems opposing. 5-HT_{1D} receptors mediates contraction in the circular layer, while 5-HT_{1B} receptors mediates contractile response to 5-HT in the longitudinal layer of the small intestine (Borman and Burleigh 1997). However, the non-selective 5-HT_1 receptor antagonist, methiothepin, does not affect the response to 5-HT on circular contractions during phase I in the small intestine (Boeckxstaens *et al.* 1990). Maybe selective novel 5-$HT_{1B/D}$ receptor antagonists (e.g. GR-127935) will be of clinical importance (De Ponti and Tonini 2001). 5-HT_{1P} receptors are present on submucous primary afferent neurons in the guinea-pig small intestine (Pan and Gershon 2000) and 5-HT_{1P} antagonists inhibits atropine, hexamethonium and xylocaine-induced phase III contractions in dog jejunum (Tohara *et al.* 2000). Further data supporting the existence and a role for the 5-HT_{1P} receptor in gut motility has been provided in rat colon, where 5-HT released by mucosal stimuli initiates peristalsis by activating sensory CGRP neurons (Grider *et al.* 1996). Whether these effects are mediated by the 5-HT_4, and not by the 5-HT_{1P} receptor, is still unclear. Finally, 5-HT_{1A} receptor agonists relax and inhibit colonic and rectal motility (Nagakura *et al.* 1996a and 1996b, De Ponti and Tonini 2001).

5-HT_2 receptor subtype

The net effect of exogenous 5-HT is contraction of the stomach and intestines, reflecting the contracting 5-HT_{2A} receptors present on smooth muscle cells (Boeckxstaens *et al.* 1990, Kuemmerle *et al.* 1995, Janssen *et al.* 2001). 5-HT activates 5-HT_{2A} and 5-HT_{2C} receptors located on postsynaptic cholinergic neurons in dog jejunum to stimulate phasic contractions and phase III activity (Graf and Sarna 1996), while the 5-HT_{2B} receptor mediates contraction of longitudinal muscle in human ileum in vitro (Borman and Burleigh 1995). 5-HT also induces colonic and rectal contractions primarily by stimulation of smooth muscle 5-HT_{2A} receptors (Prins *et al.* 1997), and by stimulation of 5-HT_{2B} receptors, which are expressed on both myenteric neurons and on smooth muscles (Borman *et al.* 2001). Despite these findings, 5-HT_2 receptor antagonists, such as ketanserin, have been without convincing effects on the motility response to 5-HT (Boeckxstaens *et al.* 1990).

5-HT_3 receptor subtype

The action of endogenous 5-HT on gastric activity is mediated partly by 5-HT_3 receptors, as ondansetron inhibits gastric phase III activity and zacopride reduces the pyloric motor response to intraduodenal hydrochloric acid (Wilmer *et al.* 1993, Haga *et al.* 1996, Nakajima *et al.* 1997). 5-HT_3 antagonists have failed to normalize gastric emptying for patients with gastric stasis or anorexia nervosa. However in reflux disease patients, 5-HT_3 receptor antagonism, using granisetron, reduce gastroesophageal reflux by improving the function of the LES (Gonlachanvit *et al.* 2001). Thus 5-HT_3 receptors seem to participate to some extend in the regulation of gastric emptying in man. Apparently stimulation of 5-HT_3 receptors or their antagonism, affects small bowel transit and motility differently according to the species and segment. In guinea pig circular muscle of small intestine, 5-HT_3 receptors play a role in the ascending excitatory reflex and these receptors may be on interneurons in the reflex pathway (Furness *et al.* 1993). In addition, ondansetron inhibits 5-HT_3-mediated ACh release in guinea-pig ileum longitudinal muscle-myenteric plexus strips (Fox and Morton 1990). In the isolated mouse ileum, 5-HT_3 receptors mediate 5-HT-induced contraction, however with a different

pharmacological profile to that reported in guinea pig ileum (Tuladhar *et al.* 2000). In the rat YM-31636, a novel selective 5-HT_3 agonist, increase GI motility, which is inhibited by ramosetron, which is a novel 5-HT_3 receptor antagonist (Kiso *et al.* 2001). In dog small intestine, activation of the 5-HT_3 receptor induce ascending contractions through an enteric excitatory pathway (Mizutani *et al.* 1992), and 5-HT_3 receptor antagonists inhibits the digestive jejunal phase III contractions (Tohara *et al.* 2000). The excitatory pathway is formed by a series of cholinergic interneurons and motorneurons, apart from the anal contraction (Mizutani *et al.* 1992). The 5-HT_3 receptor also regulates the ileocolonic junction, as 5-HT_3 receptor agonists activate an ACh-mediated contraction and a relaxation mediated by an as yet unknown non-adrenergic-non-cholinergic (NANC) neurotransmitter (Boeckxstaens *et al.* 1990). In healthy volunteers, 5-HT_3 receptor antagonists have no major impact on small intestinal transit time or mouth-to-cecum transit time (De Ponti and Tonini 2001), but selectively increase the interval between MMCs (Bush *et al.* 2000). PPY and neurotensin could be involved in this response, since the 5-HT_3 receptor antagonist, GR 38032F, reduce postprandial PPY and neurotensin plasma levels (Talley *et al.* 1989). For colonic effects, a ondansetron-sensitive mechanism participates in guinea pig (Jin *et al.* 1999) and in the physiological contractile response in the young healthy human transverse and descending colon after ingestion of a meal (der Ohe *et al.* 1994). Ondansetron by itself does not affect fasting colonic tone or phasic contractions, but antagonism of 5-HT_3 receptors blunts the gastrocolonic response, by actions on vagal afferent neurons, as well as in area postrema. Ondansetron retards colonic transit and inhibits the colonic motor response to meal in health without age or gender differences, but has no effect in diarrhea-dominated irritable bowel syndrome (D-IBS) patients (Talley *et al.* 1990). This could be because ondansetron has little effects on the increased frequency of GMCs in D-IBS (De Ponti and Tonini 2001). In carcinoid patients, ondansetron reduce postprandial colonic hypertonic response to normal level (der Ohe *et al.* 1994), suggesting ondansetron for treatment of carcinoid diarrhea. In summary, 5-HT_3 antagonists may retard colonic transit in health by altering phasic contractions. 5-HT_3 receptors, however, do not seem to be involved in the stimulation of GMCs in the colon or the small intestine. 5-HT_3 receptor antagonists may, therefore, be ineffective in retarding transit, if diarrhea is caused by an increase in the frequency of GMCs.

5-HT_4 receptor subtype

5-HT_4 receptors have been identified on myenteric neurons and muscles in the fundus, corpus and antrum of the stomach (Taniyama *et al.* 2000). 5-HT_4 receptors do not seem to directly mediate nausea and vomiting, however if these symptoms are a result of delayed gastric emptying, they may be involved. In general, 5-HT_4 receptor agonists stimulate gut motility. However, depending on the agonist, 5-HT_4 receptor agonism has varying effects on gastric motility. 5-HT_4 receptor agonists, SDZ-HTF-919 and procalopride, does not alter gastric emptying in dog or man (Nguyen *et al.* 1997, Bouras *et al.* 1999, Bouras *et al.* 2001). Tegaserod, another 5-HT_4 receptor agonist, however accelerates gastric emptying, small intestinal and maybe colonic transit in man in health (Camilleri 2001b, Degen *et al.* 2001), accelerates gastric motility in diabetic mice (Mathis *et al.* 2001b) and postoperatively in rats (Zittel *et al.* 2000). However, in constipation-predominant (C)-IBS patients, tegaserod does not change gastric emptying (Prather *et al.* 2000, De Ponti and Tonini 2001). In the intestines, relaxing 5-HT_4 receptors are present on intestinal circular and longitudinal smooth muscle cells, sensory CGRP-containing neurons (Foxx-Orenstein *et al.* 1996) and on NANC neurons, where they mediate relaxation by suppressing the amplitude and duration of phase III activity (Graf and Sarna 1996). 5-HT_4 agonism with ML-10302 evokes myoelectric activity in dog small intestine (De Ponti *et al.* 2001). However small intestinal transit is not altered by SDZ-HTF-919 in dog (Nguyen *et al.* 1997), nor by prucalopride in healthy humans (Bouras *et al.* 1999). However, tegaserod accelerates small bowel transit in healthy volunteers (Camilleri 2001b) and stimulates the peristaltic reflex and increase postoperative motility in the small intestine of rodents (Buchheit and Buhl 1991, Zittel *et al.* 2000). Tegaserod reduce orocecal transit time in C-IBS patients (Scott and Perry 1999, Camilleri 2001b), while the 5-HT_4 antagonist, SB-207266A (piboserod, now available for human studies), increase orocecal transit time towards normal in D-IBS patients (Houghton *et al.* 1999), but does not seem to affect the normal motility (De Ponti and Tonini 2001). Other 5-HT_4 agonists, such as RS-67333, dose-dependently shortens the interval of phase III on the MMC in rat (Lordal M, personal communication) and increase phase II activity in dog small intestine (Grider *et al.* 1998). SB

203-186, a selective 5-HT_4 receptor antagonist, inhibits 5-HT-induced contractions in circular muscle strips of the equine ileum (Weiss *et al.* 2002), while GR 113808, another selective 5-HT_4 receptor antagonist, itself disrupts the MMC and cause irregular spiking, but does not block the 5-HT-induced effects (Lordal M, personal communication). In the colon, 5-HT_4 agonists accelerates motility and transit in guinea pig (Jin *et al.* 1999), dogs (Nguyen *et al.* 1997), healthy volunteers and C-IBS patients (Appel *et al.* 1997, Prather *et al.* 2000, Camilleri 2001b, Lefkowitz *et al.* 2001) without cardiac side effects (Rueegg *et al.* 2001). 5-HT_4 receptors are likely to be involved in stress-induced colonic dysmotility. In dogs, prucalopride induces GMCs and causes proximal colon stimulation and distal colon inhibition of contractile motility (Briejer *et al.* 2001a). Prucalopride also accelerates colonic transit primarily by accelerating proximal colonic emptying, without affecting visceral sensitivity (Poen *et al.* 1999) in healthy human subjects (Bouras *et al.* 1999, Bouras *et al.* 2001). Prucalopride facilitates colonic motility through circular muscle relaxation and longitudinal muscle contraction (Prins *et al.* 1999, Borman *et al.* 2001). Various reports indicate that the 5-HT_4 agonists increase stool frequency in a subset of patients with idiopathic constipation, primarily in the proximal and transversing colon, by stimulating GMCs and therefore segmental contractions, but not peristalsis (Yamato *et al.* 2001). The locus for this activation is not completely known. Segmental differences could exist, as prucalopride induce GMCs and stimulates motility in the proximal colon, while inhibiting in the distal colon (Briejer *et al.* 2001b). Finally, 5-HT_4 receptors also seems involved in rectal motility, since agonism of 5-HT_4 receptors induce relaxation of canine isolated rectum smooth muscle (Prins *et al.* 1999).

In summary, 5-HT_4 receptor agonists are prokinetics and exhibit promise in accelerating gastric emptying and colonic transit, although the precise mechanism is not known, but an increase in GMC's activity is likely. 5-HT_4 agonists may act on sensory neurons, motorneurons, or interganglionic neurons to achieve these effects. The differences in effect among the 5-HT_4 agonists is probably a result of tachyphylaxis, as procalopride, which is a full agonist, seems to have less potential for tachyphylaxis than partial 5-HT_4 agonists, such as tegaserod. Similar findings are present for cisapride versus metoclopramide on gastric emptying (Camilleri 2000).

5-HT_7 receptor subtype

5-HT_7 receptors have been identified in most parts of the intestine (Hemedah *et al.* 2000, Krobert *et al.* 2001). 5-HT_7 receptor agonists relax smooth muscles in the distal gut and as such inhibits colonic and rectal motility and mediates relaxation in man (Vanhoenacker *et al.* 2000, Borman *et al.* 2001, De Ponti and Tonini 2001). It might have opposing effects in the proximal gut, since 5-HT_7 agonism induces jejunal contractions in the rat following activation of prejunctional receptors (McLean and Coupar 1996).

Mediators of 5-HT-induced motility

5-HT activates microcircuits in the ENS, which in turn initiates peristaltic reflexes (Figs 2 and 3). 5-HT-induced contraction of circular muscles is blocked completely by atropine and hexamethonium in animals, indicating that 5-HT stimulates intestinal contractions almost entirely through the release of ACh at the neuromuscular junction. However, in humans, atropine only reduces phase III activity of the MMC in the small intestine (own unpublished observations). Activation of cholinergic neurons acting at a presynaptic site and at least one nicotinic synapse seems involved (Fox and Morton 1990, Mizutani *et al.* 1992, Taniyama *et al.* 2000), while in the colon, muscarinic M_3 receptors are involved (Prins *et al.* 2001). In addition, NO (Coulie *et al.* 1999), tachykinins (Sarna *et al.* 2000) and CGRP (De Ponti and Tonini 2001) and maybe a unknown NANC neurotransmitter (Boeckxstaens *et al.* 1990) are involved as intermediate neurotransmitters for 5-HT signaling. Differences may exist between the small intestine and the colon, since tachykininergic pathways are involved in 5-HT_4 receptor agonism (ML-10302) mediating colonic motor response in the dog, but not in the small bowel (De Ponti *et al.* 2001).

5. Other neurohumoral substances (Table 1)

ACh is well described as the major regulator of gut motility mainly through muscarinic M_1 (Nelson *et al.* 1996) and M_3 receptor contractile mechanisms (Olsson and Holmgren 2001). Two types of receptors for *adenosine* coexist on smooth muscle cells of the intestines. A_2 receptors mediate relaxation through the increase of cAMP, while A_1 receptors contract due to decrease in cAMP and mobilization of Ca^{2+}. The net effect of adenosine is contraction, which can be greatly augmented if A_2 receptors are blocked (Makhlouf 1995). *Bombesin and CCK* are stimulatory transmitters of

contraction of primarily the circular layer of the intestines. However exogenous CCK relaxes the LES and the stomach, while endogenous CCK relax colonic motility (Scarpignato 1996). Part of the CCK effect is due to a concomitant release of ACh and SP. In surprise, most studies have however turned out negative for effects of CCK antagonists on improving gastric emptying (Liddle *et al.* 1986). In addition to a direct effect on the smooth muscle, also a central mechanism is likely for bombesin and CCK. As such, endogenous CCK in the paraventricular nucleus of the hypothalamus modulates colonic motility *via* CCK-B receptors (Monnikes *et al.* 2000a). This seems be a physiological effect, since CCK is mainly released by food intake. The action of CCK on intestinal motility follows a biological rhythm related to the light-dark cycle. *CGRP* is found in both the myenteric and submucous plexi and supply all layers of the intestinal wall along the entire gut (Rasmussen *et al.* 2001a). Only a small proportion can be observed in the mucosal endocrine cells, lamina propria, the muscularis mucosae, or in the circular and longitudinal outer smooth muscle layer (Timmermans *et al.* 1992). The effect of CGRP on gut motility is predominantly relaxation although the different studies indicate differences between species. For example, CGRP stimulates antral and ileal motility in the isolated perfused pig model in an atropine-sensitive, but NK_1 and NK_2 antagonist receptor antagonist-insensitive manner (Rasmussen *et al.* 2001b). Therefore, the site of excitation of CGRP on the contractile activity is probably on intramural cholinergic neurons rather than direct on the smooth muscle cells. Furthermore, CGRP seems to mediate $5\text{-}HT_4$ receptor induced afferent signals from the IPANs to induce the peristaltic reflex and motility (Grider *et al.* 1998). *CRF* is released from many sources in the body, including the CNS, the adrenal glands, immune cells, ENS and the EC cells. CRF slows gastric emptying and small intestinal transit, but increases colonic transit and defecation in healthy volunteers and causes an exaggerated colonic motility response in IBS patients (Monnikes *et al.* 2001). These actions are believed to be due to modulation of the vagal and sacral parasympathetic outflow. The mechanisms through which CRF activates colonic motor function seems to involve CRF_1 receptor activation of myenteric ganglia as well as circuitry recruiting 5-HT and mast cells (Karalis *et al.* 1991, Schafer and Mestres 1997, Fukudo *et al.* 1998, Anton 1999). The role of *cytokines* has not yet been finally established (Vrees *et al.* 2002). The involvement of *eicosanoids* in gut motility now seems clear, since cyclooxygenase (COX) inhibitors induce duodenal motility in rats, suggesting eicosanoids to exert a tonic inhibitory action on duodenal motility (Nylander *et al.* 2001). Furthermore, *prostaglandins* (PGE_2, PGI_2 and $PGF_{2\alpha}$) excite secretomotor and interneurons in the submucous plexus of the small intestine (Frieling *et al.* 1994). Two types of receptors for *leukotrienes* have been identified on gastric muscle cells, a specific receptor for leukotriene C_4 and a separate common receptor for leukotrienes D_4 and E_4. All three leukotrienes cause contraction through an increase in IP_3 and cytosolic Ca^{2+}. The influence of these agents, as for other substances (e.g. histamine and 5-HT), is likely to be most pronounced when the smooth muscle is inflamed or hypersensitized. The cells from which they are released are in proximity to muscle cells and to myenteric neurons and their terminals. These agents can act directly on muscle cells and indirectly by stimulating or inhibiting the release of neurotransmitters and in this fashion influence motility (Makhlouf 1995). *Galanin* cause relaxation of the ileum *via* action on myenteric neurons (Ren *et al.* 2001). *Gastrin* relaxes the fundus and increase gastric wall compliance (Mearadji *et al.* 1999). *GLP-1 and GLP-2* are secreted from L-cells in the distal small intestine and colon in response to ingestion. They inhibit fasting and postprandial gastric and antroduodenal motility and stimulate tonic and phasic contractile activity of the pylorus thereby probably mediating the ileal brake. They seem to mediate their effects by activating specific GLP receptors, which may also be located on neuronal structures. They inhibit cholinergic pathways probably by receptors at vagal and circumventricular organs in the CNS (Blazquez *et al.* 1998, Wettergren 2001). *Glutamate* influence gut motility but its overall effect and the receptors involved is unknown (Kirchgessner 2001). *Ghrelin*, a recently discovered peptide, stimulates gastric contractility *via* a vagal pathway (Chen *et al.* 2001). *Interleukin-1 beta* decreases ACh-induced intestinal contraction in a VIP-dependent manner (Aube *et al.* 2001). H_1 and H_2 *histamine* receptors coexist on smooth muscle cells of the gut. H_1 receptors mediate contraction and H_2 receptors mediate relaxation. The net effect of histamine is contraction, reflecting the dominant influence of H_1 receptors. This has importance for the function of the gallbladder and the sphincter Oddi (S0), as they contain neuronal plexi, that are distinct from those of the intestines (Keinke *et al.* 1986). Species differences in the neurogenic control of SO are also present. For example, in man, histamine does not change SO tone, while in pig, histamine stimulates contraction by activating H_1 receptors (Sand *et al.* 2000). Neurohumoral

agents that act at the brain level to affect gut motility include *5-HT* (5-HT_{1A} and 5-HT_2 and 5-HT_3 receptor agonists), the adrenergic system (α_2 receptor antagonists), eicosanoids (prostaglandin receptor agonists) and *dopamine* (D_1 and D_2 receptor agonists and D_2 receptor antagonist) (Gue and Bueno 1996). *Motilin* is secreted from the endocrine (EC and non-EC) cells of the mucosa of the upper jejunum. Motilin, and its agonist erythromycin, stimulates gut contractility and regulates the interdigestive motility by triggering phase III activity and increase gastric motor activity in the stomach (Bruley *et al.* 1995) and directly excites circular smooth muscle from the human colon (Van Assche *et al.* 2001). The motilin receptor has been identified as a GTP protein binding receptor, which is located throughout the ENS and on gut smooth muscles (Depoortere and Peeters 1997), with decreasing density from the stomach to the lower intestinal tract. However, a centrally mediated effect of motilin is also likely, since motilin and motilin binding sites are also present in the cortex of the brain (Depoortere and Peeters 1997, Pandolfino *et al.* 2000). Despite these findings, the precise stimulus for motilin release remains unknown (Pandolfino *et al.* 2000) and treatment of dysmotility with motilin agonists has in large been unsuccessful in studies in man. *Neurotensin* slows gastric emptying and duodenal motility (Keinke *et al.* 1986), but contracts the colon (Azriel and Burcher 2001a and 2001b). *NPY, somatostatin* and *opioids* are inhibitory transmitters as they inhibit the release of excitatory transmitters in the ENS. However, NPY applied to the hypothalamus, stimulates colonic transit by peripheral cholinergic and central CRF pathways (Monnikes *et al.* 2000b). *Opioids* are considered to exert their motor stimulatory actions through mechanisms involving μ-, δ-, κ-receptors targeting the middle part of the small intestine. β-Endorphin and morphine acts mainly trough muscular μ-receptors, while methionine-enkephalin acts *via* neuronal δ-receptors and dynorphins through neuronal κ-receptors (Makhlouf 1995). *VIP, PACAP* and *NO* all causes relaxation and a unique interplay exist between these major relaxants (Yamamoto *et al.* 1999, Ekblad and Sundler 1997a and 1997b). Neural stimulation elicits simultaneous VIP release and NO production, which results in a separate and additive effect on muscle relaxation. NO is one of the inhibitory transmitters in the NANC neurons, which regulate gut motility. NO seems to regulate the MMC pattern, since reduction of NO production in healthy volunteers triggers the onset of phase III in the small intestine (De Man *et al.* 2000, Kuiken *et al.* 2002) and in the colon (Powell and Bywater 2001). The interplay of somatostatin, opioids, and *GABA* neurons is expressed in the regulation of VIP release and NO production during the descending relaxation phase of peristalsis. GABA also relaxes the LES (Pandolfino *et al.* 2000). A recently discovered gut peptide located in human colonic myenteric neurons (Ehrhardt *et al.* 2001), *orphanin FQ/nociception*, has variable effects on stomach, small intestinal and colonic motility (Osinski and Brown 2000). *Oxytocin* is released as a neurotransmitter and excites dorsal vagal neurons in the inhibitory pathway to the stomach, while *TRH* activates the excitatory pathway to the stomach (Rogers and Hermann 1987, Wood 1995). *PACAP* is, together with NO and VIP, mediators of the inhibitory excitatory neurons and interneurons in the inhibitory arm of the peristaltic reflex in the small intestine (Camilleri 2001c). However, in the isolated model, it induces motility in the antrum of the pig stomach with a concomitant release of SP, VIP and somatostatin (Tornoe *et al.* 2001). *Secretin* is released from the mucosal S cells of the duodenum and inhibits pyloric, gastric antrum, small and large intestinal motility in addition to inducing biliary and pancreatic secretion (Leither *et al.* 1994). *Tachykinins* and their receptors are located on enteric neurons and smooth muscle cells to regulate the GMCs and retrograde contractions. SP slows small intestinal motility in the rat (Valdovinos *et al.* 1993). NK_1 receptors are located on small and large intestinal motorneurons (Bian *et al.* 2000), and colonic circular smooth muscle cells and mediate colonic GMCs, whereas NK_3 receptors are located on presynaptic neurons to mediate small intestinal GMCs (Sarna 1999) and colonic propulsion (Onori *et al.* 2001). In addition to NK_1 receptors, also NK_2 receptors have been identified directly on muscle cells, mediating contraction (Goldhill *et al.* 1999). *Xenin*, another recently discovered peptide produced by specific endocrine cells of the duodenal mucosa, induce duodenojejunal phase III activity in man in both the interdigestive and postprandial state (Feurle *et al.* 2001).

6. Whole gut motility – the importance of reflexes

Reflexes are present all the way down from the pharynx to the anus, and encounter the ENS with signaling locally and over long distances involving the prevertebral ganglia (Xie *et al.* 1997). As such prevertebral sympathetic ganglia, vagal nerves and intermesenteric nerves transmit signals for entero-

enteric inhibition and stimulation of intestinal motility (Szurszewski and Miler 1994).

The *peristaltic* reflex can be evoked by *stroking* or by circumferential *stretch*. The reflex consists of two components: descending relaxation caudal and ascending contraction oral to the site of stimulus. The contraction of the longitudinal muscle during the initial stages of filling is the "preparatory phase" and the propagating wave of the circular muscle contraction is called the "emptying phase" of peristalsis. This circular muscle activity involves myogenic, neuro-mechanical and a yet unknown mechanism (Brookes *et al.* 2001)**.** Following stroking of the mucosa, the EC cells in the mucosa releases 5-HT, which binds to receptors located on the sensory neurons. The 5-HT_3 and 5-HT_4 receptors seems to mediate at least part of this response, as for example selective 5-HT_4 agonists applied to the mucosa trigger the peristaltic reflex (Fig. 3) in human, rat and guinea-pig intestine (Grider *et al.* 1998). When activated, these sensory neurons release neurotransmitters (CGRP, ACh and SP) at the excitatory interneurons. This action along with the release of neurotransmitters from interneurons that arise distal and proximal to the area of stimulation activates the interneurons to release neurotransmitters to the excitatory and inhibitory motorneurons. The motorneurons, by the release of either ACh/tachykinins or NO/VIP, then cause the associated muscle cells to modify their spike potentials, allowing a propulsive wave to pass down the gut (Camilleri 2001a). NO provides a tonic inhibition, while the final mediator at the neuromuscular junction for the descending relaxation is probably VIP. In this manner, transmitters in the two major populations of motorneurons in the myenteric plexus regulate descending relaxation and ascending contraction. In summary, the oral excitatory component of the peristaltic reflex is probably mediated by ACh (mainly nicotinic receptors) and tachykinins (mainly SP *via* NK receptors), whereas the aboral inhibitory components is to be mediated by the release of VIP and NO. Other neurons and transmitters (for example ATP and GABA) seem to be involved in the peristaltic reflex released by stretch. This has been demonstrated in guinea-pig small intestine, where the motor response to NK_1 receptor agonists involves release of ATP in addition to NO from the inhibitory motor neurons (Lecci *et al.* 1999, Shahbazian and Holzer 2000). Stretch activates aborally projecting somatostatin neurons, which then stimulate GABA neurons. GABA is an excitatory modulator of ascending contractions in the myenteric plexus and participator of the peristaltic reflex by modulating the release of transmitters from motorneurons. Thus, release of somatostatin and GABA increase during descending relaxation, while the release of opioid decrease. This inhibited opioids activity results in VIP release and relaxation.

There is an extensive reflex modulation of gastric emptying and motor activity from distant regions of the gut and visa versa. For example, gastric distension abolishes fasting duodenal and jejunal motor activity (the *gastroenteric* reflex). The *enterogastric* reflexes involve an interaction of humoral responses with intrinsic and extrinsic (vagal) afferent and efferent neural pathways. For example, activation of 5-HT_{1A} and 5-HT_2 receptors block the duodenogastric inhibitory reflex elicited by duodenal distension (Bueno *et al.* 1997). These extended reflexes play an important role in regulating gastric emptying through excitatory or inhibitory effects on the fundus (the *enterofundus* reflex), antrum (the *enteroantral* reflex) and pylorus (the *duodenopyloric* reflex). The degree of inhibition of gastric emptying by intestinal feedback is dependent on the length and region exposed to the stimulus. During acute ileitis, as an example, contractility of the fundus is inhibited (Moreels *et al.* 2001). Maximal inhibition of liquid emptying from the stomach is seen with exposure of the most proximal 150 cm of small intestine to acid, glucose or oleic acid. This classical reflex is the *intestinal brake*, which is mediated by release of duodenal CCK, gastric gastrin, CGRP and maybe 5-HT, GLP-1, tachykinins and VIP (Olsson and Holmgren 2001). Ileal perfusion of especially lipids reduces gastric emptying, duodenal and jejunal motility and transit. These inhibitory effects define a phenomenon known as the *ileal brake*. The ileal brake probably serves a protective physiologic function to prevent the distal intestine from being overwhelmed by massive nutrient loads. In agreement with this theory, a high MMC frequency and increased cluster activity is present for patients with *short bowel syndrome* (Husebye 1999). Mediators of the ileal brake are incompletely characterized. The presence of ileal lipids in association with a meal is known to release enteroglucagon, neurotensin, and PYY, although the precise role of these mediators in the ileal brake is unknown (Husebye 1999). α_1-Adrenergic and β_1-adrenergic, CCK, opioids (naloxone) and 5-HT_3 receptor antagonists reduce ileal lipid-induced motor inhibition and an intact extrinsic innervation seems necessary to inhibit the small intestinal motility (Balsiger *et al.* 2001). A reflex circuit known as

the *vago-vagal* reflex involving the nucleus tractus solitarius, underlies moment to moment adjustments required for optimal digestive function in the upper gut. Under normal conditions, retroperistaltic contractions in the duodenum propel intestinal contents orally, known as the *duodenogastric* reflex, inducing duodenogastric reflux of bile, digestive enzymes and bicarbonate. Just as small intestinal stimulation can modulate gastric motility, perturbations of the stomach can alter small intestinal motor patterns. In contrast to the peristaltic reflex, the *intestinointestinal* reflexes are not mediated by mucosal receptors, but depends on the extrinsic innervation. Clinically, if there is distension due to mechanical obstruction or another cause, the bowel responds with a decrease in motility and tone. These intestinointestinal reflexes serve a protective function. Other inhibitory reflexes exist, such as the *peritoneogastric* reflex, which slows gastric emptying following stimulation of the peritoneum for example during a laparotomy. The *rectocolonic/rectoanal* and *colointestinal* reflexes are activated by rectal and colonic distension, respectively. They retard colonic and small bowel transit and emptying of digestants into the cecum, respectively (Makhlouf 1995, Sanders *et al.* 2000, Kunze and Furness 1999, Husebye 1999).

Only few positive forward reflexes have been identified, such as the *gastroduodeno/jejunal/ileal/colonic* reflexes, which are characterized by an increase in myoelectric, motor and propulsive activity in the intestines postprandially. The *gastroduodenoileal* reflex is abolished by intestinal transection, indicating that the reflex is mediated by intrinsic neural pathway. Another positive forward reflex is the *jejunal-ileal* reflex, which accelerates ileal motility in response to entry of chyme in the jejunum (Husebye 1999). Similar positive forward integrated motor responses includes the *colocolonic* reflex (Makhlouf 1995, Hasler 1995, Kunze and Furness 1999, Husebye 1999, Sanders *et al.* 2000).

5-HT fits perfectly the role as key mediator of most of these reflexes, as it is located in the ”tasting” EC cells of the mucosa in the whole gut and it is an important neurotransmitter for the interneurons. Tachykinins also seems important, as demonstrated in rat, where NK_1 receptors mediate the rectocolonic inhibitory reflex with the involvement of central structures (Julia *et al.* 1999).

7. Motility of the stomach

During swallowing, a vagal-mediated transient receptive relaxation occurs, followed by a more prolonged relaxation known as accommodation. However fullness and hunger is related solely to antral accommodation. The stomach can accommodate up to 2 l of fluids with no increase in pressure.

The motility patterns of the stomach is region-specific. The fundus and cardia (pacemaker region) generates tonic contractions, while the distal body and antrum exhibits phasic motor activity. Factors, in addition to age and gender, which come into play for gastric emptying includes the *volume, caloric density and osmolarity* of the injected. A 300 ml bolus of saline will empty twice as fast as a 150 ml load. In general, inert liquids empty rapidly with a time 50 % of emptying from 8 to 18 min. Liquid emptying of nutrients is tightly controlled to a rate that delivers approximately 200 kcal/h into the duodenum. Liquids with high caloric density empty more slowly than foods that have fewer calories per unit volume. An increase in osmolarity also decreases the contractility response in the small intestine. In addition to caloric density, the characteristics of the nutrient itself are important regulators of liquid emptying. Carbohydrates and most amino acids modulate intestinal nutrient delivery in part by an action on small intestinal mucosal osmoreceptors, which activate neural feedback inhibitory pathways. L-tryptophan, the precursor of 5-HT, is distinguished from the other amino acids in that it is effective at delaying liquid emptying, suggesting specific L-tryptophan receptors in the mucosa. The effect of triglycerides on gastric motility is dependent on the fatty acid chain-length with differences in their CCK-releasing ability (Hasler 1995). In spite of these experimental findings, drastic and rapid dietary changes do not seem to change gastro-duodenal motility, at least not in pigs (Boudry *et al.* 2001). The acidity of the gastric content also seems important. Omeprazol eliminates the temporal relationship between intragastric pH and characteristic of the MMC and induces delay in gastric emptying of liquid and solid meal (Rasmussen *et al.* 1999). Furthermore, the *temperature* of the injected bolus has an impact, as cold inhibits emptying.

Neurohumoral control

The neurohumoral modulation of gastric emptying for liquids and solids involves the presence of intact vagal innervation. However, vagal nerves are not necessary for the initiation or temporal co-ordination of global fasting or postprandial gastroduodenal motility patterns, but are involved in modulating the pattern of contractions during phase III. Numerous neurohumoral

substances modify the rate of gastric emptying. At least 10 different types of neurons with different transmitter combinations are involved in the excitatory control of stomach motility. Myenteric neurons of the gastric wall contain numerous neurotransmitters, including ACh, norepinephrine, 5-HT, SP, VIP, peptide histidine isoleucin (PHI) and enkephalins. Excitatory neurons contain ACh, SP or both and project directly to the circular muscle layer to control contraction. Inhibitory motorneurons contain VIP and NO and project in aboral directions to control relaxation (Olsson and Holmgren 2001).

During fasting, proximal gastric tone is maintained by vagally mediated cholinergic input. After a meal the proximal stomach relaxes probably through the activation of nitrergic neurons in the gastric wall. NO-induced relaxation involves the production of cGMP. As such, sildenafil (a selective phosphodiesterase-5 inhibitor), prolongs the activity of cGMP and thereby modifies esophageal contractions, reduce LES pressure (Zhang *et al.* 2001), inhibits interdigestive motor activity of the antrum and duodenum (Bortolotti *et al.* 2001), increases intragastric volumes after a meal and slows liquid emptying rate (Bortolotti *et al.* 2001). Conversely, a nitrergic pathway does not seem to be involved in fasting gastric tone and sensitivity to gastric distension in man (Sarnelli *et al.* 2001). Opiates of different receptor subclasses have both inhibitory and excitatory effects. 5-HT accelerates *via* 5-HT_3 receptors gastric emptying, while somatostatin, neurotensin, oxytocin, PYY, GRP, enteroglucagon, oxyntomodulin, and PGE_1 all slow gastric emptying. The role of CCK is still unclear (Hasler 1995).

Neural input from the CNS is a potent regulator of gastric motor activity and emptying. Mental stress prolongs the periodicity of the MMC. Anger increases phasic motor activity in the stomach, whereas fear and depression reduce gastric contractions. Cold pain and ischemic pain all delay gastric emptying. Multiple neural pathways are involved in these stress responses. These mediators of brain-gut interaction have been evaluated intensively. Intraventricular infusion of TRH accelerates, while CRF, CCK, opiates, bombesin, tachykinins, somatostatin, atrial natriuretic factor, GABA, calcitonin, and CGRP delays gastric emptying, partly *via* a vagal mechanism (Hasler 1995). In addition to reduce LESP and the number of transient lower esophageal sphincter relaxations (Lidums *et al.* 2000, Sifrim *et al.* 1999), GABA and 5-HT_1 receptor agonism induce gastric accommodation following activation of probably myenteric neurons (Tack *et al.* 2001, Tack and Peeters 2001).

The proximal stomach

The proximal stomach exhibits slow relaxations and contractions. The fundus relaxes for about 15 min after ingestion of a meal before returning to resting tone. This accommodation is neurally mediated and is mediated by stimulation of the tension-sensitive mechanoreceptors in the gastric wall. With surgical resection of the fundus or following fundoplication for gastroesophageal reflux disease, intragastric pressure increases and liquid emptying is enhanced. If the antrum is surgically resected, the initial phase of liquid emptying is accelerated, suggesting that the distal stomach, like the proximal part, play a role in liquid emptying. The motor activity of the duodenum also appears to regulate the rate of liquid emptying from the stomach, as enhanced liquid emptying is noted after performance of a circular myotomy of the duodenal wall.

Several neurohumoral agents have been demonstrated to relax the proximal stomach. CCK seems to be one of special importance, as CCK-8 blocks ascending contraction elicited by electrical field stimulation of duodenal mucosa by means of simultaneous activation of CCK-A and CCK-B receptors (Giralt and Vergara 2000). Other relaxants of the fundus include secretin, VIP, gastrin, somatostatin, dopamine, gastrointestinal insulin-dependent peptide, glucagon, and bombesin, whereas motilin and TRH increase pressure in the fundus (Hasler 1995, Mearadji *et al.* 1999). However, except for gastrin, their physiologic roles have not been clarified.

The distal stomach

The rhythmic synchronized contractions of the distal stomach are controlled by electrical signals generated by a pacemaker region located on the greater curvature at rate of about 3/min. While contractions of the distal stomach are always associated with gastric slow wave, the slow wave persists in the absence of gastric contractile activity. Normal fasting antral motility is cyclical and this is termed the MMC, which in average takes about 100 min (phase I – 40 min, phase II – 50 min and phase III – 10 min) (Hansen 2002). Neurohumoral pathways also affects motor activity of the distal stomach. For example stimulation of efferent vagal low-threshold fibers evokes increased antral

contractile activity that is atropine-sensitive, indicating that cholinergic inputs predominates in the antrum (Katschinski *et al.* 1996). In contrast, stimulation of high-threshold fibers decreases antral motor activity, most likely through the release of VIP and NO, with NO being the primary mediator for the muscle-relaxing effect of VIP (Murthy *et al.* 1996). VIP and PACAP are present in interneurons that project caudal within the myenteric plexus in motorneurons that project into the circular muscle layer. In the pig, PACAP 1-38 induce antral motility in an atropine- and SP antagonist-sensitive manner (Tornoe *et al.* 2001). ACh, CCK, bombesin and some of the endogenous opiates also increase antral contractions. In contrast secretin, somatostatin, glucagon, GIP, GRP, TRH, neurotensin, and PGE_2 inhibit antral motility (Hasler 1995).

The pyloric sphincter

The pyloric sphincter (PS) is a bundle of thickened circular muscles, which exhibit characteristic patterns of motility under fasting and fed conditions. During phase III of the MMC, the pylorus remains open, and fasting gastric contents are permitted to exit into the duodenum. Under fed conditions, the pylorus exhibits a complex motor response of prolonged periods of closure, with duodenal mixing and retropulsion. Relaxation of the PS is produced by strong inhibitory inputs received during gastric emptying. ICC cells interact with pyloric smooth muscle cells, and seems to act as pacemaker cells also for the pylorus. The pylorus is supplied with relatively high density of nerve fibers and neural arcs, which is quite distinct from the adjacent duodenum and distal stomach. It receives excitatory and inhibitory inputs from enteric motorneurons, which are influenced by both the extrinsic nerves, such as the vagus and sympathetics and hormonal factors. As such, electrical stimulation of the vagus results in pyloric contraction of low frequencies of stimulation and relaxation at high frequencies of stimulation, suggesting that both excitatory and inhibitory vagal pathways are present, using NO as the final mediator. In addition to NO, also VIP, PHI, galanin, PGE_1, 5-HT (all inhibitory mediators), and ACh, SP, CCK, secretin and histamine (all excitatory mediators) regulates the PS (Katschinski *et al.* 1996). Descending inhibitory pathways from the gastric antrum to the pylorus controls closure. Distension, chemical and osmolar stimulation of the duodenum activates ascending excitatory motor pathways to the antro-pyloric region and thereby slow gastric emptying by a feedback mechanism (Yuan *et al.* 2001).

8. Dysmotility of the stomach

The rapid gastric emptying in the Zollinger-Ellison syndrome exemplifies the importance of neurohumoral substances (e.g. gastrin and 5-HT) in pathology. There seems to be at least three different states of functional dyspepsia of the stomach: delayed gastric emptying (gastroparesis), impaired gastric accommodation and gastric hypersensitivity (functional dyspepsia). All these states seem to have an abnormal neurohumoral component. For example, the normally rhythmic contractions of the distal stomach are disorganized in diabetic neuropathy. Sumatriptan seems to improve several of these conditions following activation of either the $5HT_{1A}$ or $5\text{-}HT_{1P}$ receptor (Tack *et al.* 2001, Tack and Peeters 2001).

9. Motility of the small intestine

The small intestinal wall has two organized regions of muscles: the muscularis externa and the muscularis mucosa. The muscularis externa is the major effector of contractile activity. It consists of an outer longitudinal and an inner circular layer, oriented at 90 degree angle to each other. The circular layer is subdivided into inner and outer layers. The circular layer mediates the basic contractile pattern, segmentation (mixing and propulsion). The longitudinal muscle probably does not have potent propulsive capabilities, but shortens the gut length and accelerates transit. The role of the muscularis mucosa is poorly understood, but seems important for secretory processes. The interrelation between the layers remains unresolved.

The segmental and propulsive movements depend on co-ordinated contractions and relaxations of the muscle layers. Contractions may be phasic or tonic. Most contractions are phasic and are controlled by spike potentials. Relaxation results from removal of a contractile stimulus or application of an active relaxant agent. In general, relaxant agonists act through cAMP-dependent reduction in intracellular calcium levels, which results mainly in inhibition of spike potential activity (Hasler 1995).

The organized motor activity is achieved by means of segmentation (Hansen 2002). During fasting, segmentation still occurs, resulting in cleaning for undigested solids and sloughed enterocytes. Orocecal transit time for chymes is 2-4 h (Kutchai 1998). With meals low in nutrients, transit is accelerated *via* the action

of mechanoreceptors in the small intestine, while infusion of lipids causes a delay due to the action of chemoreceptors. Both these actions are inhibited by 5-HT_3 antagonists, which underline the importance of neurohumoral regulation (Read and Gwee 1994).

Because of the fibrous septum separating the duodenum from the pylorus, most of the gastric electrical activity is not propagated into the small intestine. The duodenum exhibits an electrical pacemaker distinct from that of the distal stomach and pylorus, with a dominant frequency of about 12 cycles/min. The duodenum exhibits other patterns of contractile activity in addition to propagated antroduodenal contractions (Castedal *et al.* 1997, Castedal and Abrahamsson 2001). If a surgical myotomy of the duodenum is performed, the resulting reduction in duodenal contractility is associated with enhanced distal movement of the luminal nutrients. In addition to the lower slow wave frequency in the ileum, there is a decrease in slow wave propagation velocity from about 15 cm/min in the duodenum to about 10 cm/min in the distal ileum. This phenomenon provides physiologic advantages for efficient digestion. In the proximal intestine, it is desirable to propel nutrients over a large surface area of mucosa for rapid digestion and absorption, but in the ileum, delay in propulsion permits absorption of more slowly digested and absorbed substances such as fats, bile, and fat soluble vitamins (Hasler 1995).

Neurohumoral control

The small intestine is richly supplied with sensory fibers: mechano-, chemo-, thermo- and pain receptors, which relay information through afferent fibers. Intrinsic afferent neurons that mediate local neuronal reflex activities project within the myenteric and submucous plexuses. Information from activated sensory receptors is carried in vagal and spinal afferent nerves to the CNS (Fig. 3). Most of the fibers in the vagus are afferent and synapse with neurons in the nodose ganglia. Spinal afferent fibers, carried in the splanchnic nerves, have cell bodies in the dorsal root ganglia and synapse in the dorsal horn of the spinal tract, where they activate second order neurons, which relay information back to the gut or centrally trough ascending tracts. Furthermore, most of the fibers in the splanchnic nerves are efferent. The predominant neural influence under basal conditions is inhibitory. This has clinical implications, as demonstrated in humans with spinal cord injury. These patients frequently suffer from gut dysmotility, including delayed gastric emptying and GI transit, depending on the level of the injury (Gore *et al.* 1981, Gondim *et al.* 1999).

The extrinsic supply is divided into efferent and afferent categories with information carried in parasympathetic and sympathetic nerve tracts, provided by the vagus and the splanchnic nerves. Most efferent parasympathetic and sympathetic fibers terminate in the myenteric plexus and form connections in enteric ganglia, although some sympathetic axons terminate directly on sphincteric smooth muscle.

Efferent vagal supply is maximal to the upper gut, including the proximal colon. The cell bodies of these efferent nerves reside predominantly in the vagal dorsal motor nucleus in the brain stem. The vagus nerves contain three groups of efferent fibers: preganglionic parasympathetic cholinergic nerves, which supply excitatory neurons in the enteric plexi, preganglionic cholinergic nerves, which supply inhibitory neurons in the myenteric plexus, and sympathetics from the cervical ganglia. Stimulation of efferent vagal cholinergic neurons principally activates nicotinic receptors within enteric ganglia, exiting motor activity.

Sympathetic innervation from the splanchnic nerves is different from the vagal parasympathetic innervation in that neuronal cell bodies reside outside the wall within the prevertebral ganglia (i.e. celiac, superior and inferior mesenteric ganglia). Preganglionic cholinergic neurons project from the spinal cord to the prevertebral ganglia, where they synapse through nicotinic receptors. The postganglionic neurons, which are noradrenergic, project to the enteric ganglia through the splanchnic nerves. Noradrenergic innervation from the splanchnic nerves generally inhibits excitatory cholinergic transmission within the myenteric plexus. The physiologic significance of these pathways is exemplified by the long inhibitory intestinal reflexes, which decrease motility through neural arcs involving the prevertebral ganglia.

The major intrinsic innervation to the intestinal smooth muscle project from the myenteric plexus at the interface between the longitudinal and circular layers, although the submucous plexus along the luminal aspect of the circular layer may play a minor role in the some reflex activities. The number of intrinsic neurons in the gut greatly exceeds the number of fibers in the vagus or splanchnic nerves. In humans, the ENS contains up to 100 million neurons, compared with only 2000 efferent

fibers in the vagus, suggesting that intrinsic nerves may direct most reflex and control activities and that the extrinsic innervation may serve only a modulatory function. Excitatory and inhibitory motorneurons project only a few mm along the intestine, although some fibers extend for 30 mm. Excitatory fibers in the longitudinal axis run in a cephalic direction, but inhibitory reflexes project in a caudal direction. That some reflex response of the intestine project 100 cm. or more implies that extensive interneuronal connections are involved. Most myenteric neurons project axons to other myenteric neurons and to the circular muscle, with a lesser number projecting to the submucous ganglia. Submucous ganglia are smaller than myenteric ganglia and predominantly project to the inner circular muscle layer or to the myenteric plexus (Kunze and Furness 1999).

Depending on the species and segment, myenteric motorneurons have different chemical coding. In man, almost half contain tachykinins and ACh and almost the other half contains VIP and NO with any overlap. The tachykininergic pathway mediates the excitatory neuromuscular transmission, while the VIPenergic pathway provides the inhibitory neuromuscular transmission (Shuttleworth and Keef 1995). 5-HT, somatostatin, NPY, CGRP, GRP, and galanin are co-located and function as interneurons that modulate motor activity (Hasler 1995). Due to the complexity, species differences and release of many transmitters simultaneously, it not possible always to predict the response on motility.

10. Dysmotility of the small intestine

Small intestinal dysmotility is less frequent than esophageal, gastric and colonic dysmotility. However, small intestinal motility has become the focus of investigation as a potential site for functional dyspepsia (Hansen 2002). As such, abnormal duodenal propagation patterns are present in the D-IBS (Simren *et al.* 2000). Patients with small intestinal dysmotility have a wide range of clinical manifestations, regardless of the underlying cause of the disorder. The spectrum range from asymptomatic to chronic intestinal pseudoobstruction. Common symptoms include functional dyspeptic symptoms, including intermittent postprandial epigastric or periumbilical abdominal pain, bloating, nausea, vomiting, constipation and diarrhea. Patients with small intestinal dysmotility usually have also dysmotility of other parts of the gut (Quigley 1999, Kuemmerle 2000).

Dilatation of the small intestine is a typical general feature of pathology involving small intestinal dysmotility in systematic diseases, such as scleroderma, diabetes mellitus (DM) and spinal cord injury, although the small bowel is not as frequently or severely affected as the stomach or colon. Also genetic conditions can cause dysmotility, such as familial visceral myopathies, which is characterized by fibrosis of the muscles, while familial visceral neuropathies is characterized by degeneration of the myenteric plexus (Camilleri 2001a). The etiology (Table 3) is based mainly on histology findings, using trichrome stain for the smooth muscle, and Manson's silver stain for the neurons. For example, in diabetic patients, demyelination of the proximal vagus nerve and sympathetic nerves supplying the bowel occurs, while the ENS appears to be unaffected morphologically. The functional impact on small intestinal motility has shown mixed results and actually normal MMCs are usually found in DM patients, although they suffer from gastroparesis. However, absence of intestinal phase III of the MMC has been demonstrated in some DM patients. These changes in MMC are not related to the hyperglycemia, which is known to delay gastric emptying (Quigley 1999, Hansen 2002).

11. Ileocecal junction

The ileocecal junction (ICJ) is a region of specialized smooth muscle and neural tissue. Its physiologic role seems to be to control flow of chyme from the terminal ileum to the cecum and safeguard against reflux of fecal back into the ileum. The ICJ share several properties with other sphincteric regions, like the pylorus. The vagus, the superior and the inferior mesenteric ganglia innervate the ICJ intrinsically by the myenteric plexus and extrinsically. Several neurohumoral substances exert significant effects on the ICJ. SP contracts ICJ, while 5-HT has a biphasic opposing effect. In pigs, using manometry, the ICJ displays myogenic tone, which is influenced by excitatory muscarinic and inhibitory nitrergic and β-adrenergic postganglionic pathways (Hasler 1995, Kajimoto *et al.* 2000).

Table 3. Therapy of gastrointestinal dysmotility

Contractility-reducing agents

Alfa$_2$- and β_2-adrenoceptor agonists, botulinum toxin, calcium channel blockers, CCK_A receptor antagonists, muscarinic receptor antagonists and nitrates.

Contractility-augmenting agents

Alfa$_2$- and β_2-adrenoceptor antagonists, D_2 receptor antagonists, erythromycin, $GABA_B$ receptor agonists, muscarinic receptor agonists, neostigmin, nifedipine, nitric oxide synthase inhibitors and substituted benzamides.

Developmental agents

- 5-HT_{1A} and 5-$HT_{1B/D}$ receptor agonists for functional dyspepsia and IBS.
- 5-HT_{2A} receptor agonists specific for the smooth muscle for C-IBS and 5-HT_{2A} receptor antagonists for D-IBS.
- 5-HT_3 receptor antagonists for D-IBS, non-cardiac chest pain, functional dyspepsia, carcinoid diarrhea and maybe the short-bowel syndrome.
- 5-HT_4 receptor agonists for C-IBS, GERD, gastroparesis, functional dyspepsia, ileus and pseudoobstruction.
- 5-HT_4 receptor antagonists for D-IBS and maybe the short-bowel syndrome.
- 5-HT_7 receptor agonists and antagonists for D-IBS.
- Agents active at receptors and ion channels of the interstitial cell of Cajal membrane.
- CCK_A receptor agonists and antagonists for GERD and gastroparesis.
- GABA receptor agonists for GERD.
- Motilides for gastroparesis.
- Motilin and PGE_1 receptor agonists for constipation.
- Muscarinic M_3 receptor antagonists for D-IBS.
- Neostigmin, neurotrophic factors and N-methyl-D-aspartate for slow transit constipation and C-IBS.
- Nitric oxide donors for achalasia and nitric oxide synthase inhibitors for GERD.
- Phosphodiesterase-5 inhibitor for esophageal and gastric spastic motor disorders.

Adapted from (Huizinga et al. 1997, Gaster and King 1997, Sanger et al. 1998, Sifrim et al. 1999, Pandolfino et al. 2000, Vanhoenacker et al. 2000, Lidums et al. 2000, Trevisani et al. 2000, Camilleri 2001c, De Ponti and Tonini 2001, Sarnelli et al. 2001, Thomson et al. 2001).

12. Motility and dysmotility of the colon

Two types of myoelectrical activity are documented in the colon, slow waves and spike potentials. Colonic slow wave frequencies in normal volunteers are extremely variably. Phasic pressure waves are the most common manometric phenomenon. Other types of activity includes the short spike burst, long spike burst and GMCs. Cyclic contractile activity with a periodicity of 20 to 30 min, and perhaps analogous to the MMC of small intestine, is found. The motility index is increased 20 to 30 min after a meal and remains elevated for up to 3 h. This gastrocolonic reflex remains intact after gastrectomy and vagotomy (Philips 1995) and involves neuronal and possibly hormonal mechanisms, for example CCK, which is also a stimulator of contractile activity in the colon. A variety of peptide receptors (GRP, Y2, PACAP type 1, CCK-A, neurotensin type 1, sst2, NK_1 and VIP type 2) are expressed in the human myenteric plexus suggesting a role in motility for these peptides (Rettenbacher and Reubi 2001). However, the understanding of motility and control mechanisms for motility and migrating motor activity in the colon is largely unknown and warrants studies using genetic manipulation and the development of knockout animals in which the development or synthesis of particular neurohumoral transmitter substances or receptors has been prevented (Spencer 2001).

The two main dysmotility disorders of the colon is the CIP and the IBS. Qualitative analysis of manometric recordings provides complementary evidence for these conditions (Herbst *et al.* 1997). The pathophysiologic features of CIP can be broadly

subdivided into a myopathic variety (e.g. progressive systemic sclerosis, amyloidosis, and hollow visceral myopathy) and a neuropathic variety (e.g. DM) (Philips 1995). Finally, total colonic manometry can be used as guide for surgical management of functional colonic obstruction (e.g. Hirschsprung's disease) (Martin *et al.* 2001).

13. Therapy for dysmotility

The targets for pharmacological control of gut motility are putatively numerous, such as the enteric neurons, EC cells, smooth muscle cells, ICC cells and mast cells. Finally, yet another therapeutic approach to motility disorders is to alter symptom perception without exerting a direct effect on smooth muscle contractility. It is beyond the scope of this paper to go into further presentation of these therapeutic modalities except for the overview given in Table 3.

Acknowledgements

This work was kindly supported by Sofus Carl Emil Friis and his wife Olga Friis Foundation, The Carlsberg Foundation, The Enid Ingemann Foundation, Else and Mogens Wedell-Wedellsborg Foundation, Dagmar Marshall Foundation, The Lundbeck Foundation, The Novo Nordisk Foundation, C.C. Klestrup and his wife Henriette Klestrup Foundation, The Danish Medical Association Research Foundation, and the Danish Hospital Foundation for Medical Research in Region of Copenhagen, The Faroe Islands and Greenland. I thank Novartis Healthcare A/S, Denmark, for support and help on illustrations.

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