

## The gut as a neurological organ

Peter Holzer, Rudolf Schicho, Ulrike Holzer-Petsche, and Irmgard Th. Lippe

Department of Experimental and Clinical Pharmacology, University of Graz, Austria

### Der Gastrointestinaltrakt als neurologisches Organ

**Zusammenfassung.** Wir bezeichnen den Gastrointestinaltrakt als neurologisches Organ, um die spezielle Rolle des Nervensystems bei der Steuerung der Verdauung hervorzuheben, wird der Magen-Darm-Trakt doch von fünf verschiedenen Neuronensystemen versorgt: intrinsische enterale Neurone, vagale und spinale afferente Neurone sowie parasympathische und sympathische efferente Neurone. Praktisch jeder Aspekt der Verdauungstätigkeit steht unter neuraler Kontrolle, wobei das enterale Nervensystem (ENS) die wichtigste Rolle spielt. Das ENS funktioniert wie ein Gehirn im Darm, da es unabhängig vom Zentralnervensystem die Verdauungsvorgänge programmiert und die Tätigkeit der gastrointestinalen Effektorsysteme bedarfsgerecht koordiniert. Zu diesem Zweck liefern intrinsische afferente Neurone dem ENS entsprechende Informationen aus dem Lumen, während extrinsische afferente Neurone das Zentralnervensystem über den Funktionszustand des Gastrointestinaltrakts informieren und damit zur Energie- und Flüssigkeitshomöostase des Körpers beitragen, jedoch auch die Wahrnehmung gastrointestinaler Funktionsstörungen und Schmerzen vermitteln. Die meisten funktionellen Magen- und Darmerkrankungen hängen mit einer Dysfunktion des ENS und anderer gastrointestinaler Neuronensysteme zusammen. Aus diesem Grund stellen enterale und extrinsische afferente Neurone des Gastrointestinaltrakts einen besonders wichtigen Angriffspunkt für die medikamentöse Behandlung von Magen- und Darmkrankheiten und für die damit verbundenen Beschwerden und Schmerzen dar.

**Schlüsselwörter:** Enterale Nervensystem, autonome efferente Innervation des Gastrointestinaltrakts, extrinsische afferente Innervation des Gastrointestinaltrakts, neurale Steuerung der gastrointestinalen Motorik und Sekretion, gastrointestinaler Schmerz, funktionelle Magen- und Darmerkrankungen.

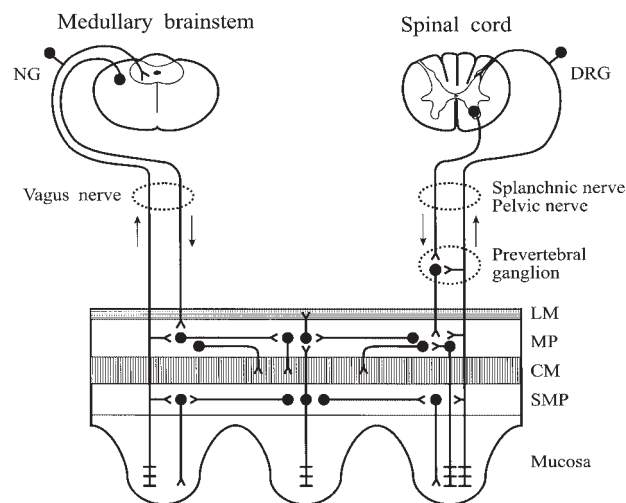
**Summary.** We refer to the gut as a neurological organ to emphasize the particular importance of the nervous system in the regulation of digestive functions, given that the gastrointestinal tract is innervated by five different classes of neurons: intrinsic enteric neurons, vagal afferents, spinal afferents, parasympathetic efferents and sympathetic efferents. Virtually each aspect of digestive

activity is under the regulatory influence of neurons, among which the enteric nervous system (ENS) plays the most important part. The ENS acts like a brain in the gut that functions independently of the central nervous system, contains programmes for a variety of gastrointestinal behaviours and governs the activity of all gastrointestinal effector systems according to need. Intrinsic sensory neurons supply the ENS with the kind of information that this system requires for its autonomic control of digestion, whereas extrinsic afferents notify the brain about any data that are relevant to energy and fluid homeostasis and the sensation of discomfort and pain. Many diseases of the gut, particularly the functional bowel disorders, seem to be related to dysfunction of the ENS and other components of the gastrointestinal innervation. The ENS and extrinsic afferents are hence prime targets for the therapeutic management of gut diseases and for the relief of the pain and discomfort associated with these disorders.

**Key words:** Enteric nervous system, autonomic efferent innervation of the gut, extrinsic sensory innervation of the gut, neural control of gastrointestinal motility and secretion, visceral pain, functional bowel disorders.

### Introduction

The physiological role of the gastrointestinal (GI) tract is to assimilate food and thus to maintain body energy, fluid and electrolyte homeostasis. Conflicting with this absorptive function through a permeable epithelium is the need to defend a huge area of mucosa against toxic, antigenic and pathogenic food contaminants and the microflora in the GI lumen. To meet with these challenges, effective digestion not only depends on metabolic and endocrine regulation but also requires immune and neural control mechanisms. Indeed, the alimentary canal is not only equipped with the most extensive immune system in the body [1, 2] but can also boast of the largest collection of neurons that is present outside the central nervous system (CNS). Thus, the GI tract is supplied by 5 different divisions of the nervous system (enteric neurons, vagal afferents, spinal afferents, parasympathetic efferents and sympathetic efferents), which are interconnected with each other and with the GI effector tissues (Fig. 1). Virtually each aspect of digestive activity is in part or totally governed by neurons. Premier in this respect is the *enteric ner-*



**Fig. 1.** Schematic diagram showing the multiple innervation of the gastrointestinal (GI) tract by intrinsic enteric neurons originating in the myenteric plexus (MP) and submucosal plexus (SMP), extrinsic sensory neurons originating from the nodose ganglia (NG; vagal afferents) and dorsal root ganglia (DRG; spinal afferents), and autonomic efferent neurons of the parasympathetic nervous system (vagus and pelvic nerves) and sympathetic nervous system (splanchnic nerves). Only a minority of the various classes of enteric neurons is shown; these neurons supply all gastrointestinal effector systems including the longitudinal muscle (LM), circular muscle (CM), mucosa and vasculature

vous system (ENS) which lies within the wall of the alimentary canal and acts like a little brain that can function independently of the CNS. The ENS issues programmes to coordinate digestion by regulating the activity of the GI effector cells and edits any input which the gut receives from the CNS via autonomic efferents.

Recognition of this abundant regulatory network of neurons and its pathophysiological relevance for the di-

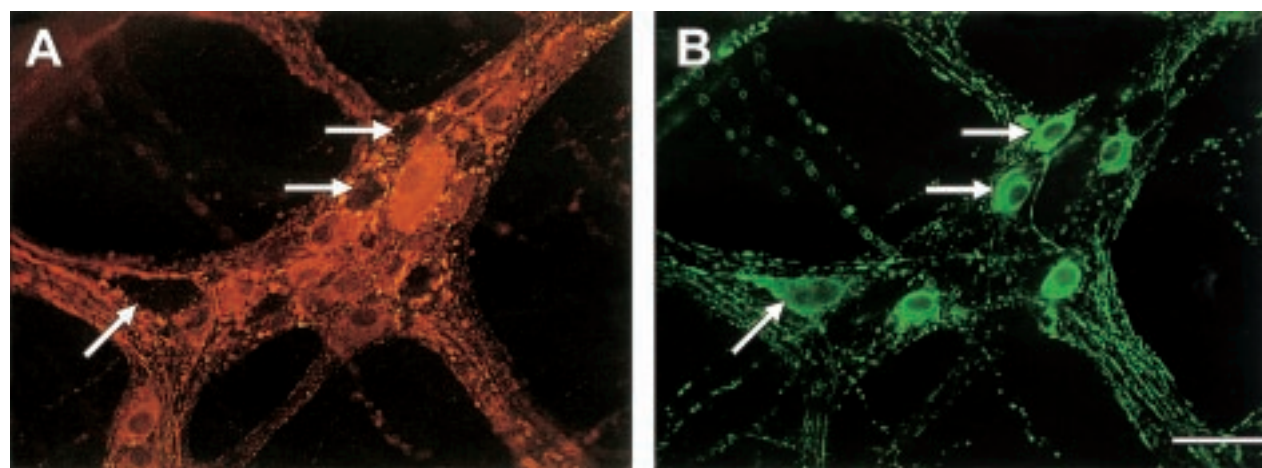
gestive system has led to the establishment of neurogastroenterology [3, 4] as a subspecialty within the field of gastroenterology. Starting off with the basic organization and functional characteristics of the GI innervation, the current overview highlights some of the most important implications of the ENS and its allied nervous systems in health and disease. It is obvious from such a functional view of the gut that the GI innervation represents a key for understanding many bowel diseases and an important target for the development of novel and effective therapies in gastroenterology.

## The enteric nervous system, a brain in the gut

### Types of enteric neurons

Functionally most important among the GI innervation is the intrinsic ENS which consists of a network of ganglia and connecting nerve strands (Fig. 2), that extends from the oesophagus to the internal anal sphincter and, in addition, projects to bile duct, gallbladder and pancreas [5, 6]. The ganglia form two major plexuses (Fig. 1), the myenteric plexus (Auerbach plexus) which lies between the longitudinal and circular muscle layer and the submucosal plexus (Meissner plexus) which in humans and large mammals consists of an external and internal plexus [5, 7]. Although the number of neurons in the individual ganglia is small and hardly ever exceeds 100 (Fig. 2), the ganglia are so numerous that the total number of enteric neurons in the GI tract is in the order of hundreds of millions [8]. With this abundance of somata, the gut contains as many nerve cells as the spinal cord [5].

Enteric neurons can be classified in terms of shape and morphology, chemical coding (cotransmitter content), connections, projections and functional properties [4-6, 9-11]. Thorough analysis of the ENS in the guinea-pig intestine has enabled Costa et al. [9] and Furness [10] to differentiate more than 15 different types of neurons (Table 1). Among these, the major classes are intrinsic primary afferent neurons (IPANs), interneurons that connect ganglia within and between the plexuses, motor neurons, se-



**Fig. 2.** Immunocytochemical demonstration of the two major neurochemical codes in the myenteric plexus of the rat stomach. **A** Neurons expressing choline acetyltransferase. **B** Neurons expressing nitric oxide synthase. These two codes are in almost all neurons mutually exclusive, and arrows indicate neurons that contain nitric oxide synthase but not choline acetyltransferase. Calibration bar: 50  $\mu$ m

**Table 1.** Summary of select neuron types in the enteric nervous system of the guinea-pig small intestine

| Origin            | Type   | Projection                       | Chemical coding                              |
|-------------------|--|----------------------------------|--|
| Myenteric plexus  | Excitatory motor neurons with <i>short</i> processes | Circular muscle                  | <b>ChAT, TK</b> , ENK, GABA                  |
|                   | Excitatory motor neurons with <i>long</i> processes  | Circular muscle                  | <b>ChAT, TK</b> , ENK, NFP                   |
|                   | Inhibitory motor neurons with <i>short</i> processes | Circular muscle                  | <b>NOS, VIP, ATP</b> , PACAP, ENK, NPY, GABA |
|                   | Inhibitory motor neurons with <i>long</i> processes  | Circular muscle                  | <b>NOS, VIP, ATP</b> , PACAP, DYN, GRP, NFP  |
|                   | Excitatory motor neurons                             | Longitudinal muscle              | <b>ChAT, TK</b> , calretinin                 |
|                   | Ascending interneurons (local motor reflexes)        | Myenteric plexus ganglia         | <b>ChAT, TK</b> , calretinin                 |
|                   | Descending interneurons (local motor reflexes)       | Myenteric plexus ganglia         | <b>ChAT, ATP</b> , NOS, VIP, GRP, NPY        |
|                   | Descending interneurons (MMC)                        | Myenteric plexus ganglia         | <b>ChAT, SOM</b>                             |
|                   | Descending interneurons (secretory reflexes)         | Myenteric plexus ganglia         | <b>ChAT, 5-HT</b>                            |
|                   | Intrinsic primary afferent neurons                   | Mucosa and muscle                | <b>ChAT, TK</b> , calbindin                  |
|                   | Intestinofugal neurons                               | Prevertebral sympathetic ganglia | <b>ChAT, GRP, VIP, CCK, ENK</b>              |
| Submucosal plexus | Noncholinergic secretomotor/vasodilator neurons      | Mucosa and submucosal arterioles | <b>VIP, GAL</b>                              |
|                   | Cholinergic secretomotor/vasodilator neurons         | Mucosa and submucosal arterioles | <b>ChAT</b> , calretinin, DYN                |
|                   | Cholinergic secretomotor neurons                     | Mucosa                           | <b>ChAT</b> , NPY, CCK, SOM, CGRP, DYN       |
|                   | Intrinsic primary afferent neurons                   | Mucosa                           | <b>ChAT, TK</b> , calbindin                  |

Data compiled from Costa et al. [9] and Furness [10]. Chemical codes **in bold** denote major transmitters. *CCK*, cholecystokinin; *CGRP*, calcitonin gene-related peptide; *ChAT*, choline acetyltransferase; *DYN*, dynorphin; *ENK*, enkephalin; *GABA*,  $\gamma$ -aminobutyric acid; *GAL*, galanin; *GRP*, gastrin-releasing peptide; 5-HT, 5-hydroxytryptamine; MMC, migrating motor complex; NFP, neurofilament protein; *NOS*, nitric oxide synthase; *NPY*, neuropeptide Y; *PACAP*, pituitary adenylate cyclase-activating peptide; *SOM*, somatostatin; *TK*, tachykinins (substance P, neurokinin A); *VIP*, vasoactive intestinal polypeptide.

cretomotor neurons, and vasodilator neurons. A further group of enteric neurons which projects to the prevertebral sympathetic ganglia (coeliac and mesenteric ganglia) is referred to as intestinofugal neurons [10, 12, 13].

The neurochemical properties (e.g., coexpression of distinct transmitters, receptors and ion channels) of enteric neurons represent an aspect whereby specific classes of enteric neurons may become amenable to selective manipulation by novel therapeutics. Acetylcholine, tachykinins such as substance P (SP) and neurokinin A (NKA), nitric oxide (NO), adenosine triphosphate (ATP), vasoactive intestinal polypeptide (VIP), neuropeptide Y (NPY), opioid peptides and 5-hydroxytryptamine (5-HT) are among the established transmitters of the ENS (Fig. 2, Table 1). Excitatory transmission within the ENS can be placed in two categories [8, 14]: fast transmission through nicotinic acetylcholine receptors, P2X purinoceptors and 5-HT<sub>3</sub> receptors, and slow transmission through muscarinic acetylcholine receptors as well as tachykinin NK<sub>1</sub> and NK<sub>3</sub> receptors. Excitatory communication from motor neurons to intestinal smooth muscle is brought about by muscarinic M<sub>3</sub> acetylcholine and tachykinin NK<sub>1</sub> and NK<sub>2</sub> receptors [15, 16], whereas inhibitory neuromuscu-

lar transmission involves fast junction potentials mediated by ATP and slow junction potentials mediated by NO and VIP [17, 18].

Depending on the class which they belong to, enteric neurons supply virtually all layers of the alimentary canal, notably the lamina propria of the mucosa, the submucosa with its dense network of blood vessels, the circular muscle layer and the longitudinal muscle sheet (Table 1). Arranged in multineuron circuits, the ENS is thus in a position to control all essential features of digestive activity. In addition, immune function and inflammatory as well as other pathological processes also are under the influence of the ENS. The physiological relevance of the ENS for gut function is highlighted by the functional deficits (Table 2) associated with developmental defects in the ENS, such as in infantile hypertrophic pyloric stenosis, total GI aganglionosis and megacolon (Hirschsprung's disease), or degeneration of enteric neurons, such as in achalasia and intestinal pseudo-obstruction [3, 19, 20]. There are multiple genes and growth factors that are essential for the normal migration of neural crest cells to the GI tract and their subsequent differentiation into enteric nerve and glial cells [21]. Hirschsprung's disease is related to defects in sev-

**Table 2.** Summary of select diseases/disorders that affect the gastrointestinal tract and are related to defects in its innervation

| Disease/disorder                        | Defective system  | Type of defect                                     |
|---|---|--|
| Achalasia                               | Myenteric plexus (oesophagus)   | Degeneration of NOS and VIP neurons                |
| Congenital oesophageal stenosis         | Myenteric plexus (oesophagus)   | Lack of NOS neurons                                |
| Infantile hypertrophic pyloric stenosis | Myenteric plexus (pylorus)  | Lack of NOS-positive circular muscle motor neurons |
| Intestinal pseudo-obstruction           | Myenteric plexus (small bowel)  | Degeneration of neurons                            |
| Hirschsprung's disease (megacolon)      | Myenteric and submucosal plexus (colon, rectum)                                   | Congenital aganglionosis                           |
| Neuronal intestinal dysplasia           | Myenteric and submucosal plexus, extrinsic autonomic innervation (whole GI tract) | Multiple abnormalities                             |
| Short small bowel syndrome              | Myenteric plexus (small bowel)  | Congenital hypoganglionosis                        |
| Myotonic dystrophy                      | Myenteric and submucosal plexus (whole GI tract)                                  | Degeneration of neurons containing SP and ENK      |
| Chagas disease                          | Myenteric and submucosal plexus (whole GI tract)                                  | Degeneration of neurons                            |
| Paraneoplastic syndrome                 | Myenteric plexus (oesophagus, stomach, small bowel)                               | Degeneration of neurons                            |
| Intestinal hypoperistalsis syndrome     | Myenteric plexus (bowel)  | Congenital hyperganglionosis                       |
| Sipple's syndrome                       | Myenteric and submucosal plexus (oesophagus, bowel)                               | Hyperganglionosis                                  |
| Diverticular disease                    | Enteric nerve fibres (colon)  | Abnormalities of circular muscle motor neurons     |
| Idiopathic (functional) constipation    | Myenteric and submucosal plexus (colon)   | Abnormalities in cell number and chemical codes    |
| Functional bowel diseases               | Extrinsic sensory and autonomic innervation (stomach, colon)                      | Functional abnormalities                           |
| Inflammatory bowel disease              | Myenteric and submucosal plexus (small bowel, colon)                              | Abnormalities in cell number and chemical codes    |
| Diabetic neuropathy                     | Myenteric plexus and extrinsic innervation (stomach, bowel)                       | Abnormalities                                      |

Data compiled from Goyal and Hirano [3] and Giaroni et al. [19]. *ENK*, enkephalin; *GI*, gastrointestinal; *NOS*, nitric oxide synthase; *SP*, substance P; *VIP*, vasoactive intestinal polypeptide.

eral genes [3, 21], a full list of which can be found in the OMIM database at <http://www.ncbi.nlm.nih.gov/omim>.

#### *Enteric nerve circuits*

In order to programme and control digestive functions, the ENS is arranged in circuits that typically are composed of IPANs, a variable number of interneurons and output neurons to the effector tissues (motor, secretomotor and vasodilator neurons). These nerve circuits exhibit several unique characteristics one of which is their polarization. Bayliss and Starling [22] were the first to recognize that localized distension elicits contraction of the circular muscle orally to the site of the stimulus and relaxation anally to it, and it is now emerging that secretory reflex circuits are organized in a similar directional manner [23]. The basis for these polarized reflexes is that the underlying nerve circuits are made of distinct circumferential, ascending and descending pathways that involve either excitatory or inhibitory output neurons.

#### *Nerve circuits controlling GI motility*

##### Patterns of GI motor activity

GI motor activity serves the storage, mixing and propulsion of ingested food, which is achieved by appropriate motor patterns that are governed both by muscular

control mechanisms and the ENS. Stationary mixing of the luminal contents is brought about by pendular movements of the longitudinal muscle and segmental contractions of the circular muscle. The rhythmicity which characterizes these nonpropulsive movements derives from a syncytial network of pacemaker cells, the interstitial cells of Cajal, which have an oscillating membrane potential that is transmitted electrically to the adjacent smooth muscle layers [24, 25]. Through these *slow waves*, the excitability of the electrically coupled smooth muscle cells undergoes phasic variations and their contractile activity is synchronized. This aspect of smooth muscle regulation is also relevant to the spatiotemporal regulation of the propulsive motility pattern of peristalsis [24, 25]. Importantly, the interstitial cells of Cajal are innervated by excitatory and inhibitory motor neurons and are thus important transducers of the ENS output to the musculature [24, 25].

Accommodation represents a mechanism whereby the gastric fundus actively relaxes in response to food intake and the stomach can store food. This receptive relaxation involves vagal and enteric reflexes that converge on a final inhibitory motor neuron of the ENS that acts by releasing NO [26–28]. Accommodation, however, also occurs in the intestine in which filling-induced distension activates circumferential and descending inhibitory reflex pathways [29].

Peristaltic propulsion of the luminal contents is the most complex motor pattern of the intestine, whose spatiotemporal coordination [30] depends on several enteric motor reflexes. Distortion of the mucosal villi and/or distension of the gut wall by a bolus of chyme triggers a contraction of the circular muscle orally, and relaxation aborally, to the site of stimulus [31, 32]. The wavelike propagation of these motor events results from successive activation of mechanosensitive enteric neurons as the bolus moves down the gut, this process being assisted by descending excitation within the ENS [3, 30, 33]. The major pathways involved in these reflexes are: ascending excitatory pathways with IPANs, interneurons and excitatory motor neurons; descending inhibitory pathways that consist of IPANs with long anal projections and inhibitory motor neurons; descending excitatory pathways with IPANs and excitatory motor neurons; and circumferential pathways involving IPANs and excitatory as well as inhibitory motor neurons.

While accommodation, pendular movements, segmental contractions and propulsive peristalsis serve the digestion of food in the postprandial period, the migrating motor complex is a motor pattern typical of the interdigestive state [34]. Following clearance of the chyme from the small intestine, the motor activity of the stomach and small intestine changes to a cyclic pattern that consists of 3 successive periods: rest (phase I), irregular activity (phase II) and propulsive peristalsis through the whole small intestine (phase III). This sequence of interdigestive motor phases is regulated both by GI hormones such as motilin and the nervous system [34, 35]. Particularly the migrating motor complex of phase III is under the control of the ENS with its peristaltic motor circuitry, and its propagation through the whole small bowel is thought to be facilitated by particular descending interneurons in the myenteric plexus (Table 1) that contain choline acetyltransferase and somatostatin [10].

#### Sensory neurons of enteric nerve circuits controlling GI motility

The motor pattern of peristalsis is triggered by IPANs that originate either in the Auerbach or Meissner plexus, have a Dogiel type II morphology with multiple axons and exhibit action potentials followed by a distinct phase of after-hyperpolarization [6, 8]. Through their mucosal chemosensors, mucosal mechanosensors and muscular tension receptors, IPANs monitor the luminal environment and motor status of the gut and thereby enable the ENS to regulate digestion according to need. By synapsing with each other, they form self-reinforcing networks that issue outputs to interneurons and effector neurons [8]. In the guinea-pig and rat small intestine, communication between the IPANs themselves and their target neurons is mediated by acetylcholine acting via nicotinic receptors and the tachykinins SP and NKA acting via NK<sub>1</sub> and NK<sub>3</sub> receptors [8, 10, 11, 36–38]. Other enteric neurotransmitters can also influence the sensory gain of the IPAN network, a mode of action whereby pituitary adenylate cyclase-activating peptide appears to stimulate intestinal peristalsis [39].

The sensory repertoire of IPANs is extended by their responsiveness to mediators released from immune and

enteroendocrine cells, which act like "taste buds" of the gut and serve as interface between the GI lumen and IPAN terminals in the lamina propria [6, 40]. The enterochromaffin (EC) cells are the major source of 5-HT in the body, contributing more than 80% to the total amine content [41]. They release 5-HT in response to certain constituents of food, mechanical distortion of the mucosal villi, bacterial products such as cholera toxin, cytostatic drugs such as cisplatin and mucosal injury [41–47]. 5-HT, in turn, stimulates IPANs of the submucosal plexus predominantly via 5-HT<sub>1P</sub> and 5-HT<sub>4</sub> receptors [43, 44, 48] and IPANs of the myenteric plexus preferentially via 5-HT<sub>3</sub> receptors [49]. Accordingly, 5-HT released from EC cells seems to be involved in the initiation of peristalsis through mucosal stimuli [43, 48] but does not contribute to peristalsis triggered by muscle stretch [49, 50].

#### Enteric motor neurons

The enteric output neurons can be broadly differentiated into those containing choline acetyltransferase (cholinergic neurons) or NO synthase (nitroergic neurons) (Fig. 2). Coexpression of additional markers yields target-specific subcodes of enteric effector neurons (Table 1), although these subcodes vary with region and species [9–11, 23, 51–53]. Being the effector of intestinal peristalsis with its aborally moving pattern of contraction and relaxation, the circular muscle is under the control of both excitatory and inhibitory motor neurons of the ENS. The excitatory motor neurons in the guinea-pig small intestine receive inputs from ascending and descending interneurons, have a Dogiel type I shape, and use acetylcholine and tachykinins as excitatory transmitters [10, 16]. Muscle contraction is brought about via muscarinic acetylcholine receptors on interstitial cells of Cajal and muscle fibres, tachykinin NK<sub>1</sub> receptors on interstitial cells and tachykinin NK<sub>2</sub> receptors on the muscle [10, 16, 24, 25, 54]. Under physiological conditions transmission via muscarinic receptors prevails, whereas tachykinins represent a backup system that maintains peristalsis once cholinergic transmission has been compromised [55].

Accommodation and descending inhibitory reflexes depend on the activity of inhibitory motor neurons that also have a Dogiel type I morphology and receive fast synaptic inputs via nicotinic acetylcholine receptors from local IPANs and noncholinergic inputs from IPANs with long descending projections [9, 10, 36]. The transmitters of inhibitory motor neurons comprise NO, ATP, VIP and carbon monoxide [9, 10], which either act directly on the muscle or indirectly via interstitial cells of Cajal [24, 25]. Being tonically active, inhibitory motor neurons control the excitability of the smooth muscle and determine when the omnipresent slow waves initiate contractions [4]. Accordingly, the absence or loss of inhibitory motor neuron activity results in tonic contracture of the muscle, which is a critical factor in the motor disturbances of achalasia, infantile hypertrophic pyloric stenosis and Hirschsprung's disease [3, 19]. The role of inhibitory motor neurons is further highlighted by the finding that blockade of inhibitory motor transmission impairs GI accommodation and disrupts intestinal peristalsis [26, 28, 56–58].

### *Enteric nerve circuits controlling GI secretion*

There is increasing awareness that the ENS is an important factor in the regulation of GI secretion of ions, mucus, enzymes, hormones and fluid [10, 59, 60]. In the stomach, the release of acid from the parietal cells and of pepsinogen from the chief cells is controlled by cholinergic secretomotor neurons which integrate signals from mucosal IPANs as well as input from vagal efferents [10, 60]. In the intestine, electrolyte and fluid secretion is governed by cholinergic and noncholinergic secretomotor neurons that originate both from the myenteric and submucosal plexus and project to the mucosa [9–11]. There are two types of cholinergic secretomotor neurons in the guinea-pig intestine, one type containing NPY and the other expressing calcitonin, and a single class of noncholinergic secretomotor neurons immunoreactive for VIP [10].

The control of GI secretion by the ENS depends on nerve circuits that involve mucosal IPANs, interneurons, and secretomotor neurons [9–11, 23]. These pathways are, in addition, modulated by sympathetic efferents which, when activated, inhibit enteric secretory reflexes [4, 10, 61]. As in motor regulation, 5-HT released from EC cells in response to chemical or mechanical stimulation of the mucosa can excite IPANs through interaction with distinct 5-HT receptors and thereby elicit secretory processes [6, 42, 44, 59, 62]. The enteric nerve circuits regulating intestinal secretion involve transmission via tachykinin NK<sub>1</sub>, NK<sub>2</sub> and NK<sub>3</sub> receptors, nicotinic and muscarinic acetylcholine receptors as well as VIP receptors [59, 63–67]. Apart from activating secretory reflexes within the ENS, IPANs may evoke secretion via release of acetylcholine and tachykinins from their mucosal processes onto the epithelium [10, 59, 64].

Particularly worth noting is that the secretory diarrhoea evoked by cholera toxin depends on enteric nerve reflexes that are initiated by 5-HT release from EC cells [42, 63, 67]. This implication of enteric nerve circuits in distinct forms of infectious diarrhoea exposes novel targets for antisecretory treatment, which is likewise relevant to the neurogenic diarrhoea elicited by rotavirus, *Clostridium difficile* toxin A and *Escherichia coli* enterotoxin [66–68].

### *Enteric control of GI microcirculation*

Cholinergic and noncholinergic neurons originating from the submucosal plexus in the guinea-pig small intestine project not only to the lamina propria of the mucosa but also issue collaterals to submucosal arterioles [9, 10]. Activation of these neurons causes arteriolar dilatation and thereby increases mucosal blood flow [69]. The parallel innervation of secretory epithelium and mucosal microvasculature suggests that stimulation of secretomotor/vasodilator neurons provides a mechanism whereby blood supply and secretory activity are balanced with each other according to the digestive state [10].

### **Extrinsic autonomic input to the gut**

The extrinsic autonomic innervation of the gut, consisting of the parasympathetic and sympathetic nervous system (Fig. 1), serves two major functions. On the one hand, the autonomic efferents participate in the reflex con-

trol of digestive functions across GI regions that are too distant to be bridged by the ENS. On the other hand, they convey messages from the CNS to the gut and thus enable the organism to balance digestive activity with the body's need of energy and fluid. It is important to realize that these efferent signals are sent primarily to the ENS which plays a key role in editing and integrating extrinsic information into its programmes governing digestion [4, 70].

### *Parasympathetic vagal efferents*

The parasympathetic efferents of the vagus nerves project exclusively to the enteric ganglia of the oesophagus, stomach and intestine where they form synapses with ENS neurons. This instance has – in J.N. Langley's outline of the autonomic nervous system – been taken to consider enteric neurons as postganglionic parasympathetic neurons [5]. Such a conception, though, is no longer tenable in view of the independent role of the ENS in the regulation of digestion [5]. Despite this autonomy of the ENS, efferent vagal neurons provide a profuse and widespread input to the myenteric plexus of the oesophagus and stomach, whereas their input to the small intestine is less extensive [70]. Reflexes involving vagal afferent and vagal efferent neurons play a prominent role in the upper GI tract where they help coordinate the motor and secretory responses to food intake. Although the transmission of efferent nerve impulses via nicotinic acetylcholine receptors results in excitation of enteric neurons, the final effector response depends on the enteric pathways that are stimulated. Thus, vagal motor reflexes can result in muscle contraction or inhibition of muscle activity, as is the case with the receptive relaxation of the gastric fundus [26, 28], whereas vagal influences on secretion in the gastroduodenal region are generally of a stimulant nature [4].

### *Sympathetic efferents*

Enteric ganglia are also the preferential projection targets of sympathetic efferents in the gut although other GI layers, notably sphincter muscles and submucosal arterioles, are directly supplied by noradrenergic axons [5, 71]. Originating mostly from prevertebral ganglia, sympathetic neurons exhibit target-specific differences in their chemical coding. In the guinea-pig intestine, noradrenergic efferents coexpressing NPY supply predominantly intestinal arterioles, while axons positive for noradrenaline and somatostatin run preferentially to submucosal ganglia, and efferents containing noradrenaline but neither of the two peptides project to the myenteric plexus [5, 72]. While sympathetic neurons can cause sphincter contraction and vasoconstriction by a direct action of their transmitters on smooth muscle, the sympathetic inhibition of digestive activity in nonsphincteric regions of the gut results primarily from interruption of excitatory enteric pathways rather than from stimulation of inhibitory enteric pathways [4, 5].

The major effect of sympathetic input to the ENS is presynaptic inhibition of transmitter release at fast and slow excitatory junctions, which causes shutdown of excitatory enteric nerve circuits governing motility and secretion [4, 5, 61, 71, 73]. In addition, noradrenaline released from sympathetic nerve fibres can directly inhibit

submucosal secretomotor neurons [59]. Since these enteric neurons also issue projections to submucosal arterioles, inhibition of their activity removes any enteric vasodilator tone, which will facilitate vasoconstriction caused by transmitter release from perivascular sympathetic nerve fibres [4]. A further antivasodilator action of noradrenergic neurons is reflected by the ability of  $\alpha_2$ -adrenoceptor stimulation to inhibit mucosal vasodilator reflexes mediated by extrinsic sensory nerve fibres [74].

The principal sympathetic transmitter noradrenaline inhibits synaptic transmission within the ENS primarily via activation of presynaptic  $\alpha_2$ -adrenoceptors. Depending on region and species, the other actions of noradrenaline in the gut involve postsynaptic  $\alpha_1$ -,  $\alpha_2$ -,  $\beta_1$ -,  $\beta_2$ - and  $\beta_3$ -adrenoceptors [71]. ATP and NPY, which are cotransmitters of sympathetic efferents as well as of certain enteric neurons, exert multiple actions on gut function. Thus, ATP causes vasoconstriction and influences GI motor activity in a complex manner [14, 75, 76] while NPY inhibits GI secretion and blocks peristaltic motility through interference with excitatory enteric motor pathways [77, 78].

### *Sympathetic reflexes*

Sympathetic efferents participate in a number of autonomic reflexes that in general cause inhibition of digestive activity, often in GI regions remote from the site of stimulation. The afferent arc of these reflexes is constituted by intestinofugal enteric or extrinsic afferent neurons, and the reflex centre lies either in the prevertebral sympathetic ganglia or in the spinal cord.

The prevertebral ganglia integrate several inputs which modify the final output of postganglionic sympathetic efferents to the gut [12, 13]. Besides signals from preganglionic efferent and intestinofugal enteric neurons, the coeliac and mesenteric ganglia also receive inputs from collaterals of spinal afferent neurons [12, 13, 40, 79–81]. Intestinofugal neurons originating from the myenteric plexus form excitatory cholinergic synapses with the somata of postganglionic sympathetic neurons that project back to the gut [12, 81, 82]. With this connection, intestinofugal neurons participate in entero-enteric reflexes that inhibit GI motility orally to the site of stimulation and thus contribute to the feedback mechanisms whereby distal parts of the intestine regulate more proximal regions from which they receive products of digestion [12, 13, 40]. The physiological significance of the sympathetic nervous system in gut function is hence often described in terms of a sympathetic brake, whose ablation in states of anaphylaxis and inflammation results in exaggerated motility and secretory diarrhoea [4, 61].

Sympathetic reflexes, being relayed either in the spinal cord or in the prevertebral ganglia (short-loop reflexes), are also relevant to the shutdown of propulsive motility under conditions of irritation and injury [83]. Adynamic (paralytic) ileus resulting from surgical trauma seems to develop in two phases. The initial halt of peristalsis is a physiological response that protects the gut from further damage and is mediated both by extrinsic sympathetic reflexes and a change in the motor programme of the ENS [83–87]. When trauma is extensive and followed by pronounced inflammation, motor blockade does not re-

solve. This second phase, which represents the pathological stage of ileus, is related not only to the neural programme of peristaltic arrest but also to shutdown of muscle excitability by excess quantities of NO that are produced by the infiltrating monocytes and neutrophils [88]. Prolonged motor stasis leads to bacterial overgrowth, which after mucosal barrier disruption may result in bacterial translocation, systemic inflammation, and multiple organ dysfunction or failure [89].

## **Extrinsic sensory innervation of the gut**

### *Vagal and spinal afferents*

Unlike other organs, the alimentary canal is supplied by a multiplicity of sensory neurons which, according to their origin, can be classified into several groups. Besides the intrinsic (enteric) sensory neurons, there are two groups of *extrinsic* primary afferent neurons that innervate the gut (Fig. 1). The *vagal* afferents originate from the jugular and nodose ganglia while the *spinal* afferents have their cell bodies in the dorsal root ganglia. It is important to realize that 80–90% of the axons in the vagus nerves are sensory nerve fibres and that hence the vagus nerve is essentially an afferent nerve [90, 91]. The spinal afferents reach the GI tract via the splanchnic and pelvic nerves in which they constitute 10–30% of all nerve fibres [90, 91]. On this route the axons pass through the prevertebral ganglia (Fig. 1) where they form, via collaterals, synapses with the sympathetic ganglion cells [12, 79, 80]. In the GI tract, the endings of vagal and spinal afferents project to the serosa, myenteric plexus, muscle, submucosa (particularly arterioles) and mucosa [40, 90–94], where they respond to alterations of the chemical environment in the lumen, interstitial space and vasculature and to changes in the mechanical properties of the gut wall such as distension, relaxation or contraction.

The parallel innervation of the gut by intrinsic and extrinsic afferents suggests that these two classes of sensory neurons serve two fundamentally different roles in GI function. Intrinsic sensory neurons supply the ENS with the kind of information that this brain of the gut requires for its independent control of digestion, whereas the extrinsic afferents supply the CNS with information that is relevant to body energy, fluid and electrolyte homeostasis, tissue integrity and the sensation of discomfort and pain. Congruent with these different roles are neuropharmacological differences in the expression of transmitters, receptors and ion channels. For instance, only extrinsic afferents express the vanilloid receptor type 1 (VR1) cation channel, and the VR1 ligand capsaicin has been particularly useful in differentiating between the functional implications of extrinsic and intrinsic afferents of the gut [95].

It has long been held that pain arising from the viscera is mediated exclusively by spinal afferents, whereas the only task of vagal afferents lies in the physiological regulation of digestive activity in the upper GI tract [90–92]. However, there is now growing awareness that vagal afferents make a distinct contribution to disease-related alterations in visceral sensation [96, 97]. Vagal afferent neurons respond to a variety of noxious chemicals [96], mediate nausea and emesis in response to various pe-

ripheral stimuli [41] and participate in the communication between the peripheral immune system and the CNS [98, 99]. Thus, the illness responses to infection and inflammation (fever, anorexia, somnolence, decrease in locomotor activity, decrease in social exploration, hyperalgesia) involve vagal afferents that react to the peripheral generation of interleukin-1 $\beta$  and other proinflammatory cytokines [98, 99].

These findings corroborate the view that sensory neurons in the vagus nerve contribute to emotional-affective and other aspects of abdominal nociception [100]. This concept has been borne out by investigations of the processing of a gastric mucosal acid insult in the rat brain. Vagal afferents signal the insult to the medullary brainstem [101] wherefrom the information is passed on to mid-brain, thalamic, hypothalamic and limbic nuclei [102]. There is, however, no activation of the insular cortex, the major cerebral representation area of afferent input from the stomach. Thus, vagal afferent signalling of an acute acid insult in the gastric mucosa does not give rise to perception of pain but leads to activation of subcortical brain nuclei that are involved in emotional, behavioural, autonomic and neuroendocrine reactions to a noxious stimulus [102].

#### *GI surveillance systems in concert*

The abundance in the sensory innervation of the gut is very much in place, since the GI mucosa is the largest external surface as it extends over an area of 200–300 m<sup>2</sup>. This vast plane is exposed not only to nutrients but also to toxins, antigens and pathogens that may come in with the ingested food and to potentially harmful secretions

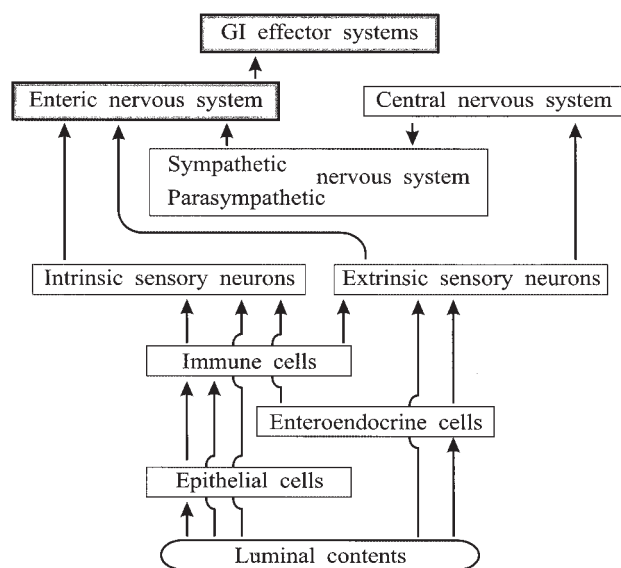
(e.g., acid and pepsin in the stomach). In addition, the alimentary canal is home to some 10<sup>13</sup> bacteria and other microorganisms which threaten to invade and translocate the gut wall [103]. To meet with these demands, the gut is endowed with an elaborate network of surveillance systems that include, besides sensory neurons, also enteroendocrine cells and immune cells (Fig. 3). These sensors act in concert to instigate the appropriate vascular, secretory and motor activities that facilitate the uptake of useful contents or dilute and rapidly expel hazardous materials through diarrhoea and/or emesis.

Enteroendocrine and immune cells are strategically positioned in the GI mucosa to analyze the luminal contents. Messenger molecules released from these cells can stimulate adjacent sensory nerve fibres which pass on the information emitted from the mucosal monitors to the ENS and CNS (Fig. 3). Prominent among the neuroactive messengers of enteroendocrine cells are 5-HT, cholecystokinin, secretin, corticotrophin-releasing factor and somatostatin [40, 47, 104]. The GI immune system includes the gut-associated lymphoid tissue, resident macrophages, eosinophils and neutrophils as well as mast cells [1, 2, 40] and chemokine-secreting epithelial cells [105]. Whenever there is microbial infection, allergy, gastroenteritis or inflammatory bowel disease, the GI immune system is called into operation and releases a host of mediators. Among them are cytokines, prostaglandins, leukotrienes, bradykinin, histamine, and serine proteases, all of which can either excite extrinsic afferent nerve fibres, in the short term, or alter their sensitivity, in the long term [40, 96, 104].

#### *Visceral discomfort and pain*

The signals that GI sensory neurons convey to the brain are normally not perceived as a conscious sensation, because they are processed only in autonomic and neuroendocrine circuits that control digestion in accordance with the body's need of energy and fluid [4, 106]. This is physiologically meaningful because there are few possibilities to voluntarily interfere with digestive functions, notable exceptions being the conscious control of food intake and the urge to have a bowel movement [106]. Many GI afferents, however, have the potential to encode noxious stimuli [96], a property that has a bearing on the discomfort and pain associated with ulcerative and inflammatory bowel diseases and functional bowel disorders (FBDs) such as noncardiac chest pain, functional dyspepsia and irritable bowel syndrome [4, 107, 108]. Given that in most cases we do not have a behavioural repertoire with which to appropriately react to painful sensations from the gut, abdominal pain is a pathological entity and not just a physiological sign of warning.

It is now hypothesized with good reason that, in FBD patients, events in the GI tract are represented in the brain in a distorted fashion, be it because there are pathological alterations in the environment of gut sensors, in the sensory gain of afferent neurons or in the central processing of afferent information from the GI tract [4, 96, 104, 106–109]. Diagnostically it is obvious that many gut reactions to physiological (e.g., food) and pathological (e.g., stress) stimuli are exaggerated and out of the normal proportion to stimulus strength [4, 104, 106, 108, 109]. This



**Fig. 3.** Schematic diagram showing the network of gastrointestinal (GI) surveillance and neural control systems that ultimately govern the activity of the enteric nervous system and the GI effector systems. The surveillance systems comprise epithelial cells, enteroendocrine cells, immune cells as well as intrinsic and extrinsic sensory neurons, which interact with each other and feed their output to the enteric nervous system, either directly or indirectly via the central and parasympathetic/sympathetic nervous systems

situation is explained by a scenario in which intense stimulation by injury, inflammation or anaphylaxis leads to accumulation of neuroactive substances in the gut wall and subsequently to functional, phenotypic and structural alterations in the GI innervation [96, 104, 108, 109]. Adaptations of this kind, which may extend far beyond the site of insult and time of original challenge, are thought to underlie the long-lasting GI hypersensitivity typical of FBDs [96, 104, 109, 110].

Visceral hypersensitivity involves peripheral and central mechanisms of sensitization, but the factors underlying GI allodynia (sensation of pain in response to stimulus strengths that normally are innocuous) and hyperalgesia (exaggerated sensation of pain in response to noxious stimulus strengths) are only in part understood [96, 104, 106, 111]. Particularly relevant to visceral pain is that most extrinsic afferents innervating the gut have the ability to sensitize [96]. As long as it is reversible, peripheral sensitization of nociceptors typically arises from modulation of nerve fibre excitability via post-translational changes such as phosphorylation of receptors, ion channels or associated regulatory proteins [112]. These processes occur when, following a mucosal insult, peripheral nociceptor terminals are exposed to a mixture of immune and inflammatory mediators [96, 104].

Persistent modifications of neuronal excitability following a visceral insult appear to be responsible for the sensory disturbances that remain after the inflammatory reaction to an insult has subsided [96, 109, 110]. Convincing evidence for such long-term adaptations has come from the observation that mechanical or chemical irritation of the colon in newborn rats leads to chronic visceral hypersensitivity in the adult animals although no pathology in the colon is discernible [113]. At the molecular level, such permanent increases in the sensory gain are related to changes in the expression of receptors, ion channels and transmitters and in the phenotype, structure, connectivity and survival of afferent neurons [112]. These persistent alterations in the properties of sensory neurons may be related to the action of neurotrophic factors which are produced in the inflamed tissue, taken up by sensory neurons and transported retrogradely to the cell bodies [112, 114].

#### *Local protective function of spinal afferents in the GI wall*

Certain spinal afferent nerve fibres are specialized in playing an efferent-like role that is brought about by transmitter release from their terminals in the wall of the GI tract. By releasing calcitonin gene-related peptide (CGRP), SP, NKA, NO and ATP from their peripheral endings, these nerve fibres act on ENS, epithelium and vasculature and thereby influence the activity of GI effector systems [59, 69, 115–118]. The functional changes include stimulation or inhibition of motility, secretion of bicarbonate, mucus and fluid, dilatation of arterioles, increase in venular permeability, degranulation of mast cells and activation of other immune cells.

The efferent-like actions of extrinsic afferents in the gut serve to alarm protective mechanisms in the face of a mucosal insult [117]. For instance, irritation of the gastroduodenal mucosa by noxious chemicals (e.g., alcohol,

nonsteroidal antiinflammatory drugs) causes backdiffusion of acid into the lamina propria and leads, via stimulation of spinal afferents, to a prompt increase in mucosal blood flow [119] and to activation of other defence mechanisms [117]. The hyperaemic reaction helps buffering the intruding acid, prevents the formation of deep erosions and ulcers [119] and assists in the healing of mucosal lesions [120]. This protective rise of blood flow is brought about by a peripheral reflex circuitry that depends on intact pathways through the coeliac ganglion and involves both CGRP and NO as mediators [117, 121–123]. A similar neural emergency system operates in the human stomach [124] and in the oesophagus, small intestine and colon of experimental animals [69, 116, 125, 126].

#### **The gut as a neurological organ: pathophysiological and therapeutic implications**

The rich supply of the GI tract by intrinsic and extrinsic neurons is crucial to normal gut function and represents a key for understanding and treating many bowel diseases [3, 4, 19]. Indeed, congenital defects in the development of the ENS, degeneration of enteric neurons or phenotypic/functional abnormalities in the GI innervation underlie a large number of GI disorders (Table 2). Idiopathic loss of inhibitory motor neurons leads to disinhibitory motor disease characterized by muscle spasms, as is the case in achalasia and intestinal pseudo-obstruction [127]. GI neuropathies may also arise from diabetes, infection (Chagas disease), inflammation (inflammatory degenerative neuropathy) and autoimmune attack of the ENS [127]. In addition, several forms of infectious diarrhoea such as those caused by cholera toxin, rotavirus, *Clostridium difficile* toxin A and *Escherichia coli* enterotoxin are brought about by initiation of secretory reflexes in the ENS [63, 66–68].

It is important to realize that the emerging view of the digestive tract as a neurological organ has implications that extend far beyond gastroenterology. Although the ENS controls the basic functions of the GI tract independently of the brain, there are reciprocal interrelationships between the ENS, the extrinsic sensory innervation, the CNS and the autonomic nervous system. Neuropathies of enteric, sensory and/or autonomic neurons are also thought to be of relevance to FBDs which are defined by chronic or recurrent abdominal symptom patterns without identifiable organic cause and clinically are related to functional disturbances of GI effector systems, autonomic dysregulation, visceral hypersensitivity and/or psychological alterations [4, 96, 106–108, 111, 128]. Interactions along this gut-brain-gut axis explain why psychological factors, stress and other life events impacting primarily on the brain can have a profound influence on GI function [4, 108, 129]. Conversely, increased signalling from the disordered gut to the brain may appreciably modify the emotional-affective status of FBD patients without necessarily giving rise to the sensation of pain.

The gut as a neurological organ implies that drugs used in neurology, psychiatry and anaesthesiology can disturb ENS function, because many of the transmitters and transmitter receptors present in the brain have also been localized to the ENS [3, 130]. This is in particular true for opiates, given that opioid peptides are expressed by en-

teric neurons and activation of opioid receptors interrupts excitatory pathways of the ENS involved in peristalsis and secretion [131]. While this antidiarrhoeal and constipative effect is a complication in the use of opiates as analgesics, it can be therapeutically exploited with drugs that, like loperamide, have a peripherally restricted site of action. Intensive care medicine has also become aware of the risks associated with the failing gut, be it the consequence of vascular hypoperfusion and/or medication with catecholamines and opiates [89]. GI ischaemia and motor stasis lead to bacterial overgrowth, which via mucosal barrier disruption and bacterial translocation may progress to multiple organ dysfunction or failure [89]. These complications can be avoided by monitoring gut function and selecting drugs with tolerable side effects on the ENS [132].

The ENS is not only a victim of unwanted drug effects but also an important target for new therapeutic strategies to manage FBDs. This is because enteric neurons express several receptors that may be stimulated or blocked in a selective manner, either because they are expressed by enteric neurons only and/or because the respective drugs are manufactured such that they cannot enter the brain. There is already a number of drugs in use or in development that act preferentially via the ENS [130]. Gastrointestinal propulsion in patients with gastroparesis can be stimulated by the prokinetic 5-HT<sub>4</sub> receptor agonist cisapride and by motilides which are motilin receptor agonists derived from erythromycin [35, 133]. Functional constipation, on the other hand, may be relieved by the enterokinetic 5-HT<sub>4</sub> receptor agonists prucalopride and tegaserod [134, 135]. Interestingly enough, brain-derived neurotrophic factor and neurotrophin-3 accelerate colonic transit and relieve constipation in humans [136]. This observation suggests that neurotrophins can be used to improve ENS function, a treatment option that holds particular potential in neurodegenerative disorders of the ENS.

Stimulation of 5-HT<sub>1B/1D</sub> receptors on nitrergic neurons in the stomach seems to be beneficial in patients with functional dyspepsia who suffer from impairment of gastric accommodation, probably because of a dysfunction of nitrergic neurons [137]. Blockade of 5-HT<sub>3</sub> receptors inhibits GI motility, and the 5-HT<sub>3</sub> receptor antagonist alosetron has offered symptomatic improvement in patients with diarrhoea-predominant irritable bowel syndrome [138]. Activation of endothelin ET<sub>B</sub> receptors [139] and cannabinoid CB<sub>1</sub> receptors [140, 141] inhibits peristalsis in vitro, but the clinical utility of endothelin ET<sub>B</sub> or cannabinoid CB<sub>1</sub> receptor antagonists in stimulating propulsive motility has not yet been addressed. Antagonists of tachykinin NK<sub>1</sub>, NK<sub>2</sub> and NK<sub>3</sub> receptors are explored for their therapeutic potential to stimulate hypomotility, reduce hypermotility and/or reverse hypersensitivity in inflammatory bowel disease and irritable bowel syndrome [142].

While drugs acting on enteric and autonomic neurons [4, 67, 128, 130] are useful for correcting functional disturbances in the gut, extrinsic afferent neurons are analyzed for molecular targets that can be utilized in the therapeutic control of the discomfort and pain associated with FBDs. Of particular interest are ionotropic chemosensors of type VR1 (capsaicin receptors), acid-sensing ion chan-

nels, P2X<sub>3</sub> purinoceptor ion channels and tetrodotoxin-resistant sodium channels of type SNS, because they are selectively expressed by extrinsic afferents. Other targets such as receptors for 5-HT, cholecystokinin, glutamate,  $\gamma$ -aminobutyric acid, tachykinins, CGRP, opioid peptides and endocannabinoids are also explored. Hitting the first element in the pain pathway, sensory neuron-targeting drugs should ideally block the exaggerated signalling of hypersensitive afferents, which implies that they aim at molecular targets that are upregulated in painful FBDs.

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#### References

1. Shanahan F (1994) The intestinal immune system. In: Johnson LR (ed) *Physiology of the gastrointestinal tract*, 3rd edn. Raven Press, New York, pp 643–684
2. Stallmach A, Zeitz M (1998) The intestine as an immunological organ. *Wien Klin Wochenschr* 110: 72–78
3. Goyal RK, Hirano I (1996) The enteric nervous system. *N Engl J Med* 334: 1106–1115
4. Wood JD, Alpers DH, Andrews PLR (1999) Fundamentals of neurogastroenterology. *Gut* 45 [Suppl II]: ii6–ii16
5. Furness JB, Costa (1987) *The enteric nervous system*. Churchill Livingstone, Edinburgh
6. Gershon MD, Kirchgessner AL, Wade PR (1994) Functional anatomy of the enteric nervous system. In: Johnson LR (ed) *Physiology of the gastrointestinal tract*, 3rd edn. Raven Press, New York, pp 381–422
7. Timmermans JP, Hens J, Adriaensen D (2001) Outer submucous plexus: an intrinsic nerve network involved in both secretory and motility processes in the intestine of large mammals and humans. *Anat Rec* 262: 71–78
8. Furness JB, Kunze WAA, Bertrand PP, Clerc N, Bornstein JC (1998) Intrinsic primary afferent neurons of the intestine. *Prog Neurobiol* 54: 1–18
9. Costa M, Brookes SJH, Steele PA, Gibbins I, Burcher E, Kandiah CJ (1996) Neurochemical classification of myenteric neurons in the guinea-pig ileum. *Neuroscience* 75: 949–967
10. Furness JB (2000) Types of neurons in the enteric nervous system. *J Auton Nerv Syst* 81: 87–96
11. Schemann M, Reiche D, Michel K (2001) Enteric pathways in the stomach. *Anat Rec* 262: 47–57
12. Szurszewski JH, Miller SM (1994) Physiology of prevertebral ganglia. In: Johnson LR (ed) *Physiology of the gastrointestinal tract*, 3rd edn. Raven Press, New York, pp 795–877
13. Miolan JP, Niel JP (1996) The mammalian sympathetic prevertebral ganglia: integrative properties and role in the nervous control of digestive tract motility. *J Auton Nerv Syst* 58: 125–138
14. Galligan JJ, LePard KJ, Schneider DA, Zhou X (2000) Multiple mechanisms of fast excitatory synaptic transmission in the enteric nervous system. *J Auton Nerv Syst* 81: 97–103
15. Maggi CA, Zagorodnyuk V, Giuliani S (1994) Specialization of tachykinin NK<sub>1</sub> and NK<sub>2</sub> receptors in produc-

- ing fast and slow atropine-resistant neurotransmission to the circular muscle of the guinea-pig colon. *Neuroscience* 63: 1137–1152
16. Holzer P, Holzer-Petsche U (1997) Tachykinins in the gut. Part I. Expression, release and motor function. *Pharmacol Ther* 73: 173–217
  17. Crist JR, He XD, Goyal RK (1992) Both ATP and the peptide VIP are inhibitory neurotransmitters in guinea-pig ileum circular muscle. *J Physiol (London)* 447: 119–131
  18. Lyster DJK, Bywater RAR, Taylor GS, Watson MJ (1992) Effects of a nitric oxide synthase inhibitor on non-cholinergic junction potentials in the circular muscle of the guinea pig ileum. *J Auton Nerv Syst* 41: 187–196
  19. Giaroni C, De Ponti F, Cosentino M, Lecchini S, Frigo G (1999) Plasticity in the enteric nervous system. *Gastroenterology* 117: 1438–1458
  20. Huizinga JD, Berezin I, Sircar K, Hewlett B, Donnelly G, Bercik P, Ross C, Algoufi T, Fitzgerald P, Der T, Riddell RH, Collins SM, Jacobson K (2001) Development of interstitial cells of Cajal in a full-term infant without an enteric nervous system. *Gastroenterology* 120: 561–567
  21. Gershon MD (1998) Genes, lineages, and tissue interactions in the development of the enteric nervous system. *Am J Physiol* 275: G869–G873
  22. Bayliss WM, Starling EH (1899) The movements and innervation of the small intestine. *J Physiol (London)* 24: 99–143
  23. Reiche D, Schemann M (1999) Mucosa of the guinea pig gastric corpus is innervated by myenteric neurones with specific neurochemical coding and projection preferences. *J Comp Neurol* 410: 489–502
  24. Huizinga JD, Robinson TL, Thomsen L (2000) The search for the origin of rhythmicity in intestinal contraction; from tissue to single cells. *Neurogastroenterol Motil* 12: 3–9
  25. Ward SM, Sanders KM (2001) Interstitial cells of Cajal: primary targets of enteric motor innervation. *Anat Rec* 262: 125–135
  26. Desai KM, Zembowicz A, Sessa WC, Vane JR (1991) Nitroergic nerves mediate vagally induced relaxation in the isolated stomach of the guinea pig. *Proc Natl Acad Sci USA* 88: 11490–11494
  27. Hennig GW, Brookes SJH, Costa M (1997) Excitatory and inhibitory motor reflexes in the isolated guinea-pig stomach. *J Physiol (London)* 501: 197–212
  28. Takahashi T, Owyang C (1997) Characterization of vagal pathways mediating gastric accommodation reflex in rats. *J Physiol (London)* 504: 479–488
  29. Waterman SA, Costa M, Tonini M (1994) Accommodation mediated by enteric inhibitory reflexes in the isolated guinea-pig small intestine. *J Physiol (London)* 474: 539–546
  30. Hennig GW, Costa M, Chen BN, Brookes SJH (1999) Quantitative analysis of peristalsis in the guinea-pig small intestine using spatio-temporal maps. *J Physiol (London)* 517: 575–590
  31. Yuan SY, Furness JB, Bornstein JC, Smith TK (1991) Mucosal distortion by compression elicits polarized reflexes and enhances responses of the circular muscle to distension in the small intestine. *J Auton Nerv Syst* 35: 219–226
  32. Grider JR, Jin JG (1994) Distinct populations of sensory neurons mediate the peristaltic reflex elicited by muscle stretch and mucosal stimulation. *J Neurosci* 14: 2854–2860
  33. Spencer NJ, Smith CB, Smith TK (2001) Role of muscle tone in peristalsis in guinea-pig small intestine. *J Physiol (London)* 530: 295–306
  34. Husebye E (1999) The patterns of small bowel motility: physiology and implications in organic disease and functional disorders. *Neurogastroenterol Motil* 11: 141–161
  35. Peeters TL (1993) Erythromycin and other macrolides as prokinetic agents. *Gastroenterology* 105: 1886–1899
  36. Johnson PJ, Bornstein JC, Burcher E (1998) Roles of neuronal NK<sub>1</sub> and NK<sub>3</sub> receptors in synaptic transmission during motility reflexes in the guinea-pig ileum. *Br J Pharmacol* 124: 1375–1384
  37. Lomax AE, Bertrand PP, Furness JB (1998) Identification of the populations of enteric neurons that have NK<sub>1</sub> tachykinin receptors in the guinea-pig small intestine. *Cell Tissue Res* 294: 27–33
  38. Mann PT, Furness JB, Southwell BR (1999) Choline acetyltransferase immunoreactivity of putative intrinsic primary afferent neurons in the rat ileum. *Cell Tissue Res* 297: 241–248
  39. Heinemann A, Holzer P (1999) Stimulant action of pituitary adenylate cyclase-activating peptide on normal and drug-compromised peristalsis in the guinea-pig intestine. *Br J Pharmacol* 127: 763–771
  40. Furness JB, Clerc N (2000) Responses of afferent neurons to the contents of the digestive tract, and their relation to endocrine and immune responses. *Prog Brain Res* 122: 159–172
  41. Andrews PLR (1994) 5-HT<sub>3</sub> receptor antagonists and antiemesis. In: King FD, Jones BJ, Sanger GJ (eds) 5-Hydroxytryptamine-3 receptor antagonists. CRC Press, Boca Raton, pp 255–317
  42. Beubler E (1995) Serotonin as an intestinal secretagogue. In: Gaginella TS, Galligan JJ (eds) Serotonin and gastrointestinal function. CRC Press, Boca Raton, pp 85–108
  43. Grider JR, Kuemmerle JF, Jin JG (1996) 5-HT released by mucosal stimuli initiates peristalsis by activating 5-HT<sub>4</sub>/5-HT<sub>1P</sub> receptors on sensory CGRP neurons. *Am J Physiol* 270: G778–G782
  44. Cooke HJ, Sidhu M, Wang YZ (1997) Activation of 5-HT<sub>1P</sub> receptors on submucosal afferents subsequently triggers VIP neurons and chloride secretion in the guinea-pig colon. *J Auton Nerv Syst* 66: 105–110
  45. Wachter CH, Heinemann A, Donnerer J, Pabst MA, Holzer P (1998) Mediation by 5-hydroxytryptamine of the femoral vasoconstriction induced by acid challenge of the rat gastric mucosa. *J Physiol (London)* 509: 541–550
  46. Gershon MD (1999) Roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment Pharmacol Ther* 13 [Suppl 2]: 15–30
  47. Raybould HE (1999) Nutrient tasting and signaling mechanisms in the gut. I. Sensing of lipid by the intestinal mucosa. *Am J Physiol* 277: G751–G755
  48. Pan H, Gershon MD (2000) Activation of intrinsic afferent pathways in submucosal ganglia of the guinea pig small intestine. *J Neurosci* 20: 3295–3309
  49. Bertrand PP, Kunze WA, Furness JB, Bornstein JC (2000) The terminals of myenteric intrinsic primary afferent neurons of the guinea-pig ileum are excited by 5-hydroxytryptamine acting at 5-hydroxytryptamine-3 receptors. *Neuroscience* 101: 459–469
  50. Tuladhar BR, Kaiser M, Naylor RJ (1997) Evidence for a 5-HT<sub>3</sub> receptor involvement in the facilitation of peristalsis on mucosal application of 5-HT in the guinea pig isolated ileum. *Br J Pharmacol* 122: 1174–1178
  51. Lomax AE, Furness JB (2000) Neurochemical classifica-

- tion of enteric neurons in the guinea-pig distal colon. *Cell Tissue Res* 302: 59–72
52. Vannucchi MG, Faussonne-Pellegrini MS (2000) NK<sub>1</sub>, NK<sub>2</sub> and NK<sub>3</sub> tachykinin receptor localization and tachykinin distribution in the ileum of the mouse. *Anat Embryol* 202: 247–255
  53. Hens J, Vanderwinden JM, De Laet MH, Scheuermann DW, Timmermans JP (2001) Morphological and neurochemical identification of enteric neurones with mucosal projections in the human small intestine. *J Neurochem* 76: 464–471
  54. Lavin ST, Southwell BR, Murphy R, Jenkinson KM, Furness JB (1998) Activation of neurokinin 1 receptors on interstitial cells of Cajal of the guinea-pig small intestine by substance P. *Histochem Cell Biol* 110: 263–271
  55. Holzer P, Lippe IT, Heinemann A, Barthó L (1998) Tachykinin NK<sub>1</sub> and NK<sub>2</sub> receptor-mediated control of peristaltic propulsion in the guinea-pig small intestine *in vitro*. *Neuropharmacology* 37: 131–138
  56. Ciccocioppo R, Onori L, Messori E, Candura SM, Cocchini T, Tonini M (1994) Role of nitric oxide-dependent and -independent mechanisms in peristalsis and accommodation in the rabbit distal colon. *J Pharmacol Exp Ther* 270: 929–937
  57. Waterman SA, Costa M (1994) The role of enteric inhibitory motoneurons in peristalsis in the isolated guinea-pig small intestine. *J Physiol (London)* 477: 459–468
  58. Holzer P, Lippe IT, Lotfi Tabrizi A, Lénárd L, Barthó L (1997) Dual excitatory and inhibitory effect of nitric oxide on peristalsis in the guinea pig intestine. *J Pharmacol Exp Ther* 280: 154–161
  59. Cooke HJ, Reddix RA (1994) Neural regulation of intestinal electrolyte transport. In: Johnson LR (ed) *Physiology of the gastrointestinal tract*, 3rd edn. Raven Press, New York, pp 2083–2132
  60. Lloyd KCK, Debas HT (1994) Peripheral regulation of gastric acid secretion. In: Johnson LR (ed) *Physiology of the gastrointestinal tract*, 3rd edn. Raven Press, New York, pp 1185–1226
  61. Xia Y, Hu H-Z, Liu S, Ren J, Zafirov DH, Wood JD (1999) IL-1 $\beta$  and IL-6 excite neurons and suppress nicotinic and noradrenergic neurotransmission in guinea-pig enteric nervous system. *J Clin Invest* 103: 1309–1316
  62. Johnson PJ, Bornstein JC, Furness JB, Woollard DJ, Orman-Rossiter SL (1994) Characterization of 5-hydroxytryptamine receptors mediating mucosal secretion in guinea-pig ileum. *Br J Pharmacol* 111: 1240–1244
  63. Jodal M, Holmgren S, Lundgren O, Sjöqvist A (1993) Involvement of the myenteric plexus in the cholera toxin-induced net fluid secretion in the rat small intestine. *Gastroenterology* 105: 1286–1293
  64. Holzer P, Holzer-Petsche U (1997) Tachykinins in the gut. Part II. Roles in neural excitation, secretion and inflammation. *Pharmacol Ther* 73: 219–263
  65. Moore BA, Vanner S, Bunnett NW, Sharkey KA (1997) Characterization of neurokinin-1 receptors in the submucosal plexus of guinea pig ileum. *Am J Physiol* 273: G670–G678
  66. Lundgren O, Peregrin AT, Persson K, Kordasti S, Uhnöo I, Svensson L (2000) Role of the enteric nervous system in the fluid and electrolyte secretion of rotavirus diarrhea. *Science* 287: 491–495
  67. Farthing MJ (2000) Novel targets for the pharmacotherapy of diarrhoea: a view for the millenium. *J Gastroenterol Hepatol* 15 [Suppl S]: G38–G45
  68. Castagliuolo I, LaMont JT, Letourneau R, Kelly C, O'Keane JC, Jaffer A, Theoharides TC, Pothoulakis C (1994) Neuronal involvement in the intestinal effects of *Clostridium difficile* toxin A and *Vibrio cholerae* enterotoxin in rat ileum. *Gastroenterology* 107: 657–665
  69. Vanner S, Surprenant A (1996) Neural reflexes controlling intestinal microcirculation. *Am J Physiol* 271: G223–G230
  70. Berthoud H-R, Patterson LM, Zheng H (2001) Vagal-enteric interface: vagal activation-induced expression of c-Fos and p-CREB in neurons of the upper gastrointestinal tract and pancreas. *Anat Rec* 262: 29–40
  71. De Ponti F, Giaroni C, Cosentino M, Lecchini S, Frigo G (1996) Adrenergic mechanisms in the control of gastrointestinal motility: from basic science to clinical applications. *Pharmacol Ther* 69: 59–78
  72. Costa M, Furness JB (1984) Somatostatin is present in a subpopulation of noradrenergic nerve fibres supplying the intestine. *Neuroscience* 13: 911–919
  73. Paton WDM, Vizi ES (1969) The inhibitory action of noradrenaline and adrenaline on acetylcholine output by guinea-pig ileum longitudinal muscle strips. *Br J Pharmacol* 35: 10–28
  74. Holzer P, Painsipp E (2001) Differential effects of clonidine, dopamine, dobutamine, and dopexamine on basal and acid-stimulated mucosal blood flow in the rat stomach. *Crit Care Med* 29: 335–343
  75. Zagorodnyuk V, Maggi CA (1998) Pharmacological evidence for the existence of multiple P2 receptors in the circular muscle of guinea-pig colon. *Br J Pharmacol* 123: 122–128
  76. Heinemann A, Shahbazian A, Barthó L, Holzer P (1999) Different receptors mediating the inhibitory action of exogenous ATP and endogenously released purines on guinea-pig intestinal peristalsis. *Br J Pharmacol* 128: 313–320
  77. Saria A, Beubler E (1985) Neuropeptide Y (NPY) and peptide YY (PYY) inhibit prostaglandin E<sub>2</sub>-induced intestinal fluid and electrolyte secretion in the rat jejunum *in vivo*. *Eur J Pharmacol* 119: 47–52
  78. Holzer P, Lippe IT, Barthó L, Saria A (1987) Neuropeptide Y inhibits excitatory enteric neurons supplying the circular muscle of the guinea pig small intestine. *Gastroenterology* 92: 1944–1950
  79. Green T, Dockray GJ (1988) Characterization of the peptidergic afferent innervation of the stomach in the rat, mouse, and guinea-pig. *Neuroscience* 25: 181–193
  80. Lindh B, Hökfelt T, Elfvin L-G (1988) Distribution and origin of peptide-containing nerve fibers in the celiac superior mesenteric ganglion of the guinea-pig. *Neuroscience* 26: 1037–1071
  81. Sharkey KA, Lomax AE, Bertrand PP, Furness JB (1998) Electrophysiology, shape, and chemistry of neurons that project from guinea pig colon to inferior mesenteric ganglia. *Gastroenterology* 115: 909–918
  82. Messenger JP, Furness JB (1993) Origins of enteric nerve cells projecting to the superior and inferior mesenteric ganglia of the guinea-pig. *Cell Tissue Res* 271: 333–339
  83. Furness JB, Costa M (1974) Adynamic ileus, its pathogenesis and treatment. *Med Biol* 52: 82–89
  84. Holzer P, Lippe IT, Holzer-Petsche U (1986) Inhibition of gastrointestinal transit due to surgical trauma or peritoneal irritation is reduced in capsaicin-treated rats. *Gastroenterology* 91: 360–363
  85. Barquist E, Bonaz B, Martinez V, Rivier J, Zinner MJ,

- Tache Y (1986) Neuronal pathways involved in abdominal surgery-induced gastric ileus in rats. *Am J Physiol* 270: R888–R894
86. De Winter BY, Boeckxstaens GE, De Man JG, Moreels TG, Herman AG, Pelckmans PA (1997) Effect of adrenergic and nitrenergic blockade on experimental ileus in rats. *Br J Pharmacol* 120: 464–468
  87. Wood JD (1999) Enteric nervous control of motility in the upper gastrointestinal tract in defensive states. *Digest Dis Sci* 44 [Suppl 8]: 44S–52S
  88. Kalff JC, Schraut WH, Billiar TR, Simmons RL, Bauer AJ (2000) Role of inducible nitric oxide synthase in post-operative intestinal smooth muscle dysfunction in rodents. *Gastroenterology* 118: 316–327
  89. Herbert MK, Holzer P, Roewer N (eds) (1999) Problems of the gastrointestinal tract in anesthesia, the perioperative period, and intensive care. Springer, Berlin Heidelberg New York Tokyo
  90. Grundy D, Scratcherd T (1989) Sensory afferents from the gastrointestinal tract. In: Schultz SG (ed) *Handbook of physiology. Section 6: The gastrointestinal system, vol I. Motility and circulation, part 1*. American Physiological Society, Bethesda, pp 593–620
  91. Sengupta JN, Gebhart GF (1994) Gastrointestinal afferent fibers and sensation. In: Johnson LR (ed) *Physiology of the gastrointestinal tract, 3rd edn*. Raven Press, New York, pp 483–519
  92. Cervero F (1994) Sensory innervation of the viscera: peripheral basis of visceral pain. *Physiol Rev* 74: 95–138
  93. Berthoud H-R, Neuhuber WL (2000) Functional and chemical anatomy of the afferent vagal system. *Auton Neurosci* 85: 1–17
  94. Phillips RJ, Powley TL (2000) Tension and stretch receptors in gastrointestinal smooth muscle: re-evaluating vagal mechanoreceptor electrophysiology. *Brain Res Rev* 34: 1–26
  95. Holzer P (1991) Capsaicin: cellular targets, mechanisms of action, and selectivity for thin sensory neurons. *Pharmacol Rev* 43: 143–201
  96. Gebhart GF (2000) Pathobiology of visceral pain: molecular mechanisms and therapeutic implications. IV. Visceral afferent contributions to the pathobiology of visceral pain. *Am J Physiol* 278: G834–G838
  97. Holzer P, Michl T, Jovic M, Heinemann A, Schuligoi R (2000) Essential role of vagal afferents in the central signalling of a gastric mucosal acid insult. In: Krammer HJ, Singer MV (eds) *Neurogastroenterology. From the basics to the clinics*. Kluwer, Dordrecht, pp 697–707
  98. Dantzer R, Bluthé RM, Layé S, Bret-Dibat JL, Parnet P, Kelley KW (1998) Cytokines and sickness behavior. *Ann NY Acad Sci* 840: 586–90
  99. Maier SF, Goehler LE, Fleshner M, Watkins LR (1998) The role of the vagus nerve in cytokine-to-brain communication. *Ann NY Acad Sci* 840: 289–300
  100. Traub RJ, Sengupta JN, Gebhart GF (1996) Differential c-fos expression in the nucleus of the solitary tract and spinal cord following noxious gastric distention in the rat. *Neuroscience* 74: 873–884
  101. Schuligoi R, Jovic M, Heinemann A, Schöninkle E, Pabst MA, Holzer P (1998) Gastric acid-evoked c-fos messenger RNA expression in rat brainstem is signaled by capsaicin-resistant vagal afferents. *Gastroenterology* 115: 649–660
  102. Michl T, Jovic M, Heinemann A, Schuligoi R, Holzer P (2001) Vagal afferent signaling of a gastric mucosal acid insult to medullary, pontine, thalamic, hypothalamic and limbic, but not cortical, nuclei of the rat brain. *Pain* 92: 19–27
  103. Autenrieth IB (1999) The human intestinal microflora: physiology and pathophysiology. In: Herbert MK, Holzer P, Roewer N (eds) *Problems of the gastrointestinal tract in anesthesia, the perioperative period, and intensive care*. Springer, Berlin Heidelberg New York Tokyo, pp 108–117
  104. Buéno L, Fioramonti J, Delvaux M, Frexinos J (1997) Mediators and pharmacology of visceral sensitivity: from basic to clinical investigations. *Gastroenterology* 112: 1714–1743
  105. Kagnoff MF, Eckmann L (1997) Epithelial cells as sensors for microbial infection. *J Clin Invest* 100: 6–10
  106. Mayer EA (1995) Gut feelings: what turns them on? *Gastroenterology* 108: 927–931
  107. De Ponti F, Malagelada J-R (1998) Functional gut disorders: from motility to sensitivity disorders. A review of current and investigational drugs for their management. *Pharmacol Ther* 80: 49–88
  108. Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE (eds) (2000) *Rome II. The functional gastrointestinal disorders, 2nd edn*. Degnon Associates, McLean
  109. Collins SM (1996) The immunomodulation of enteric neuromuscular function: implications for motility and inflammatory disorders. *Gastroenterology* 111: 1683–1699
  110. Spiller RC, Jenkins D, Thornley JP, Hebden JM, Wright T, Skinner M, Neal KR (2000) Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute *Campylobacter* enteritis and in post-dysenteric irritable bowel syndrome. *Gut* 47: 804–811
  111. Cervero F, Laird JMA (1999) Visceral pain. *Lancet* 353: 2145–2148
  112. Woolf CJ, Salter MW (2000) Neuronal plasticity: increasing the gain in pain. *Science* 288: 1765–1768
  113. Al-Chaer ED, Kawasaki M, Pasricha PJ (2000) A new model of chronic visceral hypersensitivity in adult rats induced by colon irritation during postnatal development. *Gastroenterology* 119: 1276–1285
  114. Lewin GR (1996) Neurotrophins and the specification of neuronal phenotype. *Philos Trans R Soc Lond B Biol Sci* 351: 405–411
  115. Maggi CA (1995) Tachykinins and calcitonin gene-related peptide (CGRP) as co-transmitters released from peripheral endings of sensory nerves. *Prog Neurobiol* 45: 1–98
  116. Holzer P, Barthó L (1996) Sensory neurons in the intestine. In: Geppetti P, Holzer P (eds) *Neurogenic inflammation*. CRC Press, Boca Raton, pp 153–167
  117. Holzer P (1998) Neural emergency system in the stomach. *Gastroenterology* 114: 823–839
  118. Barthó L, Lénárd L, Lázár Z, Maggi CA (1999) Connections between P2 purinoceptors and capsaicin-sensitive afferents in the intestine and other tissues. *Eur J Pharmacol* 375: 203–210
  119. Holzer P, Livingston EH, Guth PH (1991) Sensory neurons signal for an increase in rat gastric mucosal blood flow in the face of pending acid injury. *Gastroenterology* 101: 416–423
  120. Takeuchi K, Ueshima K, Ohuchi T, Okabe S (1994) The role of capsaicin-sensitive sensory neurons in healing of HCl-induced gastric mucosal lesions in rats. *Gastroenterology* 106: 1524–1532

121. Holzer P, Lippe IT (1992) Gastric mucosal hyperemia due to acid back-diffusion depends on splanchnic nerve activity. *Am J Physiol* 262: G505–G509
122. Li D-S, Raybould HE, Quintero E, Guth PH (1992) Calcitonin gene-related peptide mediates the gastric hyperemic response to acid back-diffusion. *Gastroenterology* 102: 1124–1128
123. Lippe IT, Holzer P (1992) Participation of endothelium-derived nitric oxide but not prostacyclin in the gastric mucosal hyperaemia due to acid back-diffusion. *Br J Pharmacol* 105: 708–714
124. Yeoh KG, Kang JY, Yap I, Guan R, Tan CC, Wee A, Teng CH (1995) Chili protects against aspirin-induced gastroduodenal mucosal injury in humans. *Digest Dis Sci* 40: 580–583
125. Bass BL, Trad KS, Harmon JW, Hakki FZ (1991) Capsaicin-sensitive nerves mediate esophageal mucosal protection. *Surgery* 110: 419–426
126. Reinshagen M, Patel A, Sottili M, French S, Sternini C, Eysselein VE (1996) Action of sensory neurons in an experimental rat colitis model of injury and repair. *Am J Physiol* 270: G79–G86
127. Wood JD (2000) Neuropathy in the brain-in-the-gut. *Eur J Gastroenterol Hepatol* 12: 597–600
128. Tougas G (2000) The autonomic nervous system in functional bowel disorders. *Gut* 47 [Suppl IV]: iv78–iv80
129. Taché Y, Martinez V, Million M, Wang L (2001) Stress and the gastrointestinal tract. III. Stress-related alterations of gut motor function: role of brain corticotropin-releasing factor receptors. *Am J Physiol* 280: G173–177
130. Tack J (2000) Receptors of the enteric nervous system: potential targets for drug therapy. *Gut* 47 [Suppl IV]: iv20–iv22
131. Kromer W (1990) Endogenous opioids, the enteric nervous system and gut motility. *Digest Dis* 8: 361–373
132. Fruhwald S, Scheidl S, Toller W, Petnehazy T, Holzer P, Metzler H, Hammer HF (2000) Low potential of dobutamine and dopexamine to block intestinal peristalsis as compared with other catecholamines. *Crit Care Med* 28: 2893–2897
133. Briejer MR, Akkermans LM, Schuurkes JA (1995) Gastrointestinal prokinetic benzamides: the pharmacology underlying stimulation of motility. *Pharmacol Rev* 47: 631–651
134. Bouras EP, Camilleri M, Burton DD, Thomforde G, McKinzie S, Zinsmeister AR (2001) Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder. *Gastroenterology* 120: 354–360
135. Camilleri M (2001) Review article: tegaserod. *Aliment Pharmacol Ther* 15: 277–289
136. Coulie B, Szarka LA, Camilleri M, Burton DD, McKinzie S, Stambler N, Cedarbaum JM (2000) Recombinant human neurotrophic factors accelerate colonic transit and relieve constipation in humans. *Gastroenterology* 119: 41–50
137. Tack J (2000) The physiology and the pathophysiology of the gastric accommodation reflex in man. *Verh K Acad Geneesk Belg* 62: 183–207
138. Bardhan KD, Bodemar G, Geldof H, Schutz E, Heath A, Mills JG, Jacques LA (2000) A double-blind, randomized, placebo-controlled dose-ranging study to evaluate the efficacy of alosetron in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 14: 23–34
139. Shahbazian A, Holzer P (2000) Regulation of guinea pig intestinal peristalsis by endogenous endothelin acting at ETB receptors. *Gastroenterology* 119: 80–88
140. Heinemann A, Shahbazian A, Holzer P (1999) Cannabinoid inhibition of guinea-pig intestinal peristalsis via inhibition of excitatory and activation of inhibitory neural pathways. *Neuropharmacology* 38: 1289–1297
141. Izzo AA, Mascolo N, Tonini M, Capasso F (2000) Modulation of peristalsis by cannabinoid CB1 ligands in the isolated guinea-pig ileum. *Br J Pharmacol* 129: 984–990
142. Holzer P (1998) Implication of tachykinins and calcitonin gene-related peptide in inflammatory bowel disease. *Digestion* 59: 269–283

Correspondence: Prof. Dr. Peter Holzer, Institut für Experimentelle und Klinische Pharmakologie, Universität Graz, Universitätsplatz 4, A-8010 Graz, Austria,

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