Biochimica et Biophysica Acta 1822 (2012) 85–92

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Mast cell–nerve axis with a focus on the human gut ☆,☆☆,★

Sabine Buhner, Michael Schemann *

Human Biology, Technische Universität München, Germany

ARTICLE INFO

Article history:
Received 21 February 2011
Received in revised form 7 June 2011
Accepted 10 June 2011
Available online 17 June 2011

Keywords:
Mast cell
Enteric nervous system
Viszeral afferents
Human
Neuro-immune interaction

ABSTRACT

This paper summarizes the current knowledge on the interactions between intestinal mast cells, enteric neurons and visceral afferents which are part of the gut brain axis. The focus of this review is on the relevance of the mast cell–nerve axis in the human intestine. Similarities and important differences in the organization of the mast cell–nerve axis between human and rodents are discussed. Functionally important human mast cell mediators with neural actions in the human ENS are histamine (H1-4 receptors), proteases (PAR1 receptors), several cytokines and chemokines and probably also serotonin (5-HT_3 receptors). On the other hand, mediator release from human intestinal mast cells is modulated by neuropeptides released from enteric and visceral afferent nerves. This article is part of a Special Issue entitled: Mast Cells in Inflammation.

1. Purpose of this review

Over the last decades neuroimmune interactions in the gut became a hot topic in neurogastroenterology. The components consist of different systems including various immune cells and the enteric nervous system as well as extrinsic vagal or spinal afferent nerves. The current concepts on neuroimmune interactions in the gut are almost exclusively based on data from cellular or organ responses in animal models. A number of recent reviews elegantly summarized such findings and the interested reader is referred to them [1–5]. We like to review primarily the evidence for the functional mast cell–nerve axis in the human gut. However, we will also point out findings from animal studies if they are particularly pertinent with respect to translation to the human gut or to stress the relevance for similar mechanistic studies in the human gut.

2. The enteric nervous system

The concept of a "brain in the gut" emerged in the early 1900s. Subsequently, neurochemical, neurobiological and functional studies have confirmed that the enteric nervous system (ENS) closely resembles the central nervous system. The ENS contains about 100 million nerve cells within the gut wall. It regulates autonomously most of the physiological functions of the gastrointestinal tract for example motility, secretion, microcirculation as well as immune function and thereby inflammatory processes. The basic organization and function of the ENS in all mammals is much the same. The enteric neurons are anatomically and functionally organized into three major plexuses, the myenteric, the submucous and the mucous plexus. The myentric plexus is positioned between the longitudinal and the circular muscle layers and plays an important role in regulating gut motility. The submucous plexus, being prominent only in the intestine, is located between the circular muscle layer and the mucosa. In larger species it consists of two and in human of at least three ganglionated layers. Together with the mucous plexus it is mainly involved in the interplexal communication and secretory functions. The ENS communicates with the central nervous system through sympathetic and parasympathetic efferent neurons as well as through afferent neurons which run together with parasympathetic or spinal nerve bundles [6–9]. Both efferent and afferent nerve fibers ramify substantially once they enter the gut wall. They can thereby make not only contact with enteric neurons but also with immune cells including mast cells. The functional consequence of this close anatomical association is that neurons and immune cells act as a surveillance network.

In general, the neurochemistry in the human ENS is as complex as in other species [10–12]. More than two dozens of putative neurotransmitters have been described. Neurons usually express a combination of different neurotransmitters. A few substances serve as primary transmitters which are more or less uniformly found in the same groups of enteric neurons across the species, e.g. acetylcholine (ACh), serotonin (5-HT), substance P (SP), and vasoactive intestinal polypeptide (VIP). Data available on electrophysiological properties of the human enteric neurons are still rare. Work of the last decade

☆ This article is part of a Special Issue entitled: Mast Cells in Inflammation.
☆☆ Grant support: This study is supported by the EU FP7 — IPODD Consortium and the Deutsche Forschungsgemeinschaft DFG Sche-267/7-2.
★ Financial disclosure: None to disclose; Conflicts: No conflict of interest exists.
* Corresponding author at: Human Biology, Technische Universität München, Liesel-Beckmann-Strasse 4, 85350 Freising-Weihenstephan, Germany. Tel.: +49 8161 715483; fax: +49 8161 715785.
E-mail address: schemann@wzw.tum.de (M. Schemann).

0925-4439/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbadis.2011.06.004

monitoring enteric nerve activity by means of multisite optical recording technique (MSORT) opened a way to directly study ENS activity from human tissues which was not possible up till then [13].

3. The mast cell

3.1. Mast cell origin

Cells of the mucosal immune system are typically classified as belonging to either the adaptive or the innate immune system. Mast cells are part of the innate immune system that provides the first line of defense against threatening environmental influences. In addition to their prominent role in immunoglobulin E (IgE)-dependent hypersensitivity, mast cells release and modulate the release of cytokines, growth factors, chemokines and other mediators, which in turn regulate multiple important biological processes. Mast cells are located in tissues that form large host barriers such as skin, respiratory and intestinal mucosa. In the human gastrointestinal tract mast cell density is highest in the lamina propria mucosae, where they amount to 2–3% of all cells, and slightly less (about 1% of all cells) in the submucosa. In the muscle layers or in the serosa they occur only sporadically in healthy individuals [14].

Mature mast cells show a strong species and organ specific heterogeneity concerning morphology, biochemical properties and function. Their development, differentiation, and functional reactivity are critically dependent on the microenvironment. Mast cells are extremely plastic and adapt synthesis and release of their mediators to tissue conditions. Thus when comparing research data on mast cells, the mast cell source and the particular maturation stage must be always kept in mind, and, most importantly, should be specified [15–17]. This is of special importance in terms of the profound species difference in mast cell properties between humans and rodents [18,19]. Since rodents represent the main animal models for immunological as well as neurophysiological studies, translation of data to human is difficult. Thus the tools in human mast cell research should be chosen with caution. Different methods and techniques have been recently reviewed and discussed in detail as for example the preparation of human cord blood cells, or mast cell lines as the non-transformed leukemia derived cell lines [18]. However, for studies on human intestinal mast cells, primary cultures of mast cells isolated from solid tissues seem to be a very important tool [18].

3.2. Mast cell activation

Mast cells exert their biological functions almost exclusively by the release of mediators after activation. Generally, the classical and most effective activation of mast cells occurs by interaction of a multivalent antigen with its specific IgE antibody bound to the cell membrane via the high-affinity receptor FcεRI. The knowledge on IgE independent triggers of mast cell activation, especially in humans, is very limited [19]. There are reports on Toll-like receptor mediated effects but also non-Toll-like receptor mediated effects as cholera toxin and α-haemolysin mediated human mast cell activation [20–22]. The role of cytokines seems to be of particular importance. Human mast cells challenged to interferon γ (IFNγ) express FcγRI at sufficient levels to enhance mediator release [23]. Other mediators as anaphylatoxins (C3a, C5a), nerve growth factor (NGF), interleukin 8 (IL-8) or the neuropeptide SP only affect human skin mast cells but failed to show effects on isolated human mucosal mast cells [24,25]. However, if primed by growth factors such as stem cell factor (SCF) and IL-4 these cells start to express neurokinin 1 (NK1) receptors and under these conditions then respond to SP with increased mediator release [24,26]. Co-stimulatory signals from other substances in the milieu must be considered. Sometimes, as in the case of IL-4, cytokines may not act directly but synergistically with SCF to enhance mast cell development and to alter mediator release [27–30]. In rodents similar mechanisms have been recently shown for the macrophage inflammatory protein-1α (MIP-1α) [31]. In mice MIP-1α is required for an optimal mast cell degranulation. Also inhibitory mechanisms, balancing the agonistic activity have been reported. For example, Transforming growth factor beta 1 (TGF-β1) dose dependently inhibited SCF dependent growth of human intestinal mast cells by both enhancing apoptosis and decreasing proliferation [32]. Similar inhibitory effects have been shown in human cord blood-derived mast cells for IL-10 and β2-adrenoceptor agonists [33].

The strikingly high number and diversity of mediators released from human mast cells reflect their broad actions in a wide variety of physiological and pathophysiological functions (Table 1). The mediators can be subdivided mainly into two classes. The first class includes signaling molecules that are preformed, stored as granules and can therefore be released within seconds, this is the case for as histamine, proteases and to some degree for tumor necrosis factor α (TNFα). Others are newly synthesized when mast cells become activated such as lipid mediators and most cytokines. Thus degranulation of mast cells produces a microenvironment which may in turn feed back and influence the degree of activation of mast cells. For example in human intestinal mast cells TGF-β1 was found to influence the mediator profile by reducing histamine, cysteinyl-leukotrienes, and TNFα release whereas prostaglandin D2 (PGD_2) generation and cyclooxygenase 1 and 2 expression were up regulated [32].

4. Signaling from nerves to mast cells: nerve–mast cell signaling

Extrinsic afferent nerves, in addition to transmit information to the central nervous system, carry out many local effector functions through axon collaterals within the gut wall. Endings of extrinsic afferent nerves as well as enteric neurons are in close proximity to mast cells (Fig. 1). An estimated 70% of intestinal mucosal mast cells are in direct contact with nerves, and another 20% are within 2 μm [34,35]. This anatomical association has functional relevance as communication between nerves and mast cells is crucial for maintaining mucosal homeostasis and for ensuring an appropriate response to injury. Mast cells respond to neurotransmitters and nerves thereby can regulate their activation threshold [36]. A preliminary study in guinea-pig ileum and colon preparations provided direct evidence for a spinal afferent–mast cell–ENS interaction [37]. The authors found that

Table 1
Human mast cell mediators.

Preformed in granules	De novo synthesized
Enzymes/proteoglycans	*Cytokines and growth factors*
Heparin	IL-1, IL-1R antagonist, IL-3, IL-4[a], IL-5, IL-6, IL-8, IL-9, IL-10,
Chondroitinsulfates	IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-18, TNFα, TNFβ,
Tryptases (α, β, γ)	INFα, basic FGF, VEGF, NGF, NT-3, LIF, LTβ, GM-CSF, M-CSF,
Chymase	MIF, SCF, EGF, PDGF-AA, PDGF-BB,
Carboxypeptidase-A	
Cathepsin	
Major basic protein	
Histamine	*Eicosanoids*
	PGD2, LTB4, LTC4, LTD4, PAF
	Chemokines
	CCL1, CCL2 (MCP-1), CCL3 (MIP-1α), CCL3L1, CCL4 (MIP-1β), CCL5, CCL7, CCL8, CCL11, CCL13, CCL16, CCL17, CCL20, CCL22, CXCL1, CXCL2, CXCL3, CXCL10, XCL1,
	Others
	Nitric oxide, superoxide, CRF, urocortin

Some cytokines and growth factors can be both, released from preformed pools and newly synthesized (e.g. TNF and VEGF). Table is based on data summarized in Refs. [18,19,127,128].

[a] IL-4 production seem to be restricted to mast cells of allergic persons [126].

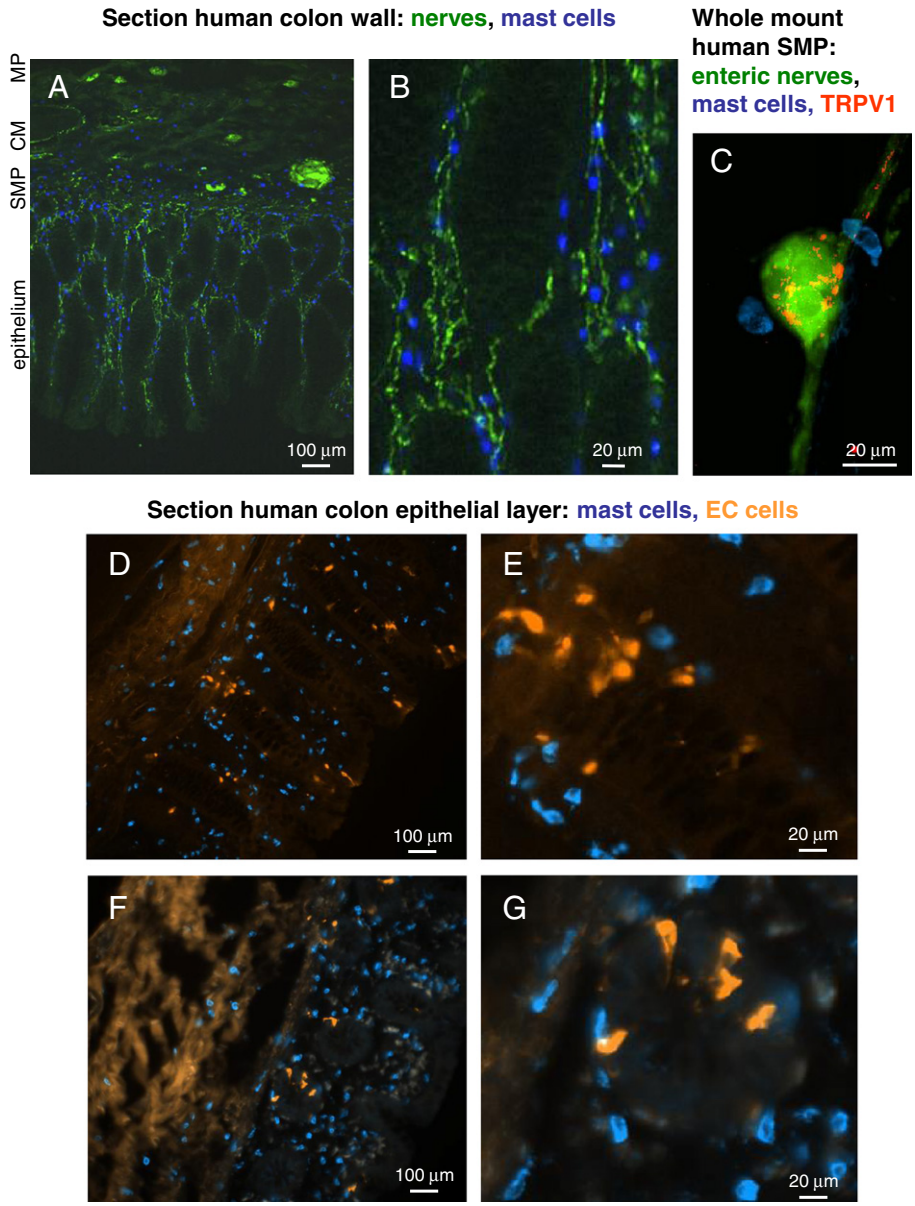

Fig. 1. Immunohistochemical demonstration of mast cell nerve interactions and mast cell phenotype in the human colon. (A): A section through the colon wall stained for the panneuronal marker PGP9.5 (in green) and mast cell tryptase (blue). Note the gradient of mast cells with the highest density in the epithelial/subepithelial layer. (B): A high power magnification of a region shown in (A) illustrating the close association between mast cells and nerves. (C) is a labeling in a whole mount illustrating the close association between enteric neurons (PGP9.5 in green), mast cells (in blue) and nerve endings of visceral afferents labeled with a TRPV1 antibody (in red). Note the two mast cells nearby the small enteric ganglion and the TRPV1 nerve fiber. (D–F) demonstrate the lack of serotonin staining (in red) in mast cells which have been labeled with mast cell tryptase (blue color in D and E) or c-kit (blue color in F and G). The staining with a serotonin antibody revealed enterochromaffine cells (EC cells). E and G are magnified regions from D and F, respectively. Note that no mast cell is serotonin-positive. SMP = submucous plexus; CM = circular muscle; MP = myenteric plexus.

stimulation of spinal afferents causes release of mast cell proteases which in turn activate submucous neurons through the protease-activated receptor 1 (PAR1) and PAR2.

The enormous variety of response patterns is suggested to be due to species and organ specific properties. At the same time, the mast cell is viewed as an enormously plastic and adaptable cell type changing its phenotype with alterations in issue conditions, pathological states or modes of stimulation. Moreover, studies reporting on mast cell mediator release are based on experiments with cell lines, isolated and cultured mast cells, tissue mast cells or indirectly suggested by pharmacological intervention with mast cell mediator actions on end organ responses or animal behavior. It therefore needs to be considered that not all the different behavior of rodent versus human intestinal mast cells is due to different intrinsic or genotypic properties. Rodent mucosal mast cells respond to adenosine triphosphate (ATP), somatostatin, calcitonin gene-related peptide (CGRP) and SP [2–4,24]. In contrast, in isolated cultured human intestinal mucosal mast cells most of these neuropeptides and transmitters had no effect on histamine release [24]. Experimental conditions may partly explain the differences. For example, when primed by SCF or IL-4 intestinal mast cells start to express NK1 receptors and respond to SP with degranulation and mediator release [26].

There is strong evidence for functional relevance of such a "sensitizing milieu". Incubation of colorectal biopsies from patients with active Crohn's Disease (CD) or Ulcerative Colitis (UC) with SP induce mast cell degranulation and histamine release from inflamed and not-inflamed tissue [38]. However, in a smaller patient group, these data could not be confirmed [24]. Others suggested that SP induced mucosal mast cell degranulation may be mediated by a receptor independent mechanism [39]. Other studies stress an increase in SP positive neurons

and their close proximity to activated mast cells in colonic mucosa of patients with irritable bowel syndrome (IBS) [40–42]. Interestingly, in cases of coexistence of IBS with interstitial cystitis a similar association between SP positive nerves and mast cell was found in the bladder wall [41]. In a rodent model the use of an NK1 receptor blocker or the blockade of enteric neurotransmission with tetrodotoxin (TTX), as well as the application of a mast cell stabilizer prevented the acute inflammatory response to Clostridium difficile toxin A [43–46]. In a murine colitis model the administration of NK1 receptor antagonist prevented among other signs of inflammation mucosal infiltration by mast cells [47]. Therefore, as suggested by Barbara et al. 2006 [48], it seems that mast cells are attracted by nerves upon the release of neuropeptides. Data so far support the concept that SP plays a role in the signal transmission from enteric neurons to mast cells in humans. Whether or not this mechanism is receptor mediated (NK1) or receptor independent remains to be clarified. The classical concept would suggest that SP is released from enteric neurons or extrinsic afferents nerves. However, a population of tryptase containing human intestinal mast cells expresses SP [49] which may also suggest a possible autocrine action of SP.

Considerable evidence suggests that also the neuropeptide VIP plays a role in pathology of inflammatory bowel diseases [2,11,50,51]. A significant increase in VIP content [52] and an increase in the population of VIP positive neurons have been shown in colonic biopsies of patients with Crohn's disease [11]. The latter study additionally describes a pronounced hypertrophy of CGRP positive, putative extrinsic sensory neurons. In inflammatory bowel diseases (IBD) the number and reactivity of enteric mast cells are increased. However direct effects of VIP or CGRP on human enteric mast cells are unknown. In mice CGRP was found to degranulate mucosal mast cells. [53]. Studies in rodents provide evidence for direct effects of various neuropeptides on mast cells, e.g. for ATP, which mediates mast cell degranulation or somatostatin which has an inhibitory influence on mast cells in rats [54].

5. Stress and mast cell signaling

Stress is associated with gastrointestinal symptoms such as diarrhea or abdominal pain. A brain–mast cell interaction is one plausible mechanism linking stress and gastrointestinal symptoms. In rodents many findings support the concept of a CNS–mast cell axis and the role of the cholinergic enteric or vagal nerves in these pathways (recently reviewed in detail [55]). In humans the release of mast cell proteases into the lumen of the small intestine occurs as a conditioned response to cold pain stress. The stress induced release of tryptase and histamine, but not PGD_2, was larger in food-allergic patients than in healthy volunteers [56]. Central nervous influences on intestinal mast cells could be mediated by extrinsic sensory nerves. While an activation of sympathetic neurons certainly accounts for the cardiovascular symptoms associated with stress, degranulation of human enteric [57] and lung mast cells [58] is rather prevented than promoted by sympathetic activation. In isolated human intestinal mast cells catecholamines and β2 adrenoreceptor agonists suppress the IgE dependent release of mediators as well as mast cell proliferation and migration [59]. In contrast, vagal stimulation in rodents [55,60] or ACh application to human lung mast cells [61] promote histamine release from mast cells. It is known, that also the corticotropin releasing factor (CRF) is mainly involved stress induced alterations of gut functions [62]. Cultured human mast cells (leukemic mast cell line and umbilical cord blood-derived mast cells) express CRF receptors, activation of which led to a release of mast cell mediators [63].

6. Signaling from mast cells to nerves: mast cell–nerve signaling

The mast cell–ENS axis combines specialized memory and sensory functions of the enteric mast cells with the capacity of the ENS to integrate paracrine signals. The role of the mast cell is twofold. On one hand it operates as a sensory cell activated by both immune and non-immune stimuli, and at the same time it acts as an effector cell releasing a number of highly biologically active mediators [64]. These substances serve as paracrine signals to extrinsic and intrinsic neural networks in the gut wall which in turn respond by initiating defense programs. A classical example for such a communication between mucosal mast cells and enteric neurons is the hypersensitivity reactions associated with food allergy. The mechanisms have been elegantly studied in a guinea pig model with antigen sensitization to cow's milk [65–69]. These data are relevant for similar interactions in the human gut. An antigen-evoked mast cell degranulation in the small and large intestine starts an immediate reaction characterized by mucosal hypersecretion [67,69] and strong muscle contractions [70]. The application of TTX suppresses the response clearly demonstrating the participation of neurons. Electrophysiological methods were used to investigate electrical and synaptic behavior of intestinal neurons during antigen exposure in milk sensitized guinea pigs. The application of the antigen to sensitized preparations strongly increased the neuronal activity in secretomotor neurons of the ENS. The effects were inhibited by a mast cell stabilizer, a histamine H2 receptor antagonist, a cyclooxygenase (COX) or a lipoxygenase inhibitor [68].

Augmented stimulation of secretomotor neurons may be also involved in the secretory diarrhea associated with food allergy in humans [5]. This is supported by the therapeutic success of using mast cell stabilizers like ketotifen to reduce the gastrointestinal symptoms in food allergy [19,71]. Recently we provided further evidence for a mast cell–ENS interaction in humans [72]. In this study we applied a mast cell mediator "cocktail", which was released from isolated human intestinal mast cells by IgE receptor cross linking, onto human enteric neurons. The "cocktail" evoked a strong neuronal excitation in preparations of human and guinea pig submucous plexus [72]. The prominent excitatory effects agree with the hyperexcitable state of enteric nerves in the inflamed gut [73]. Interestingly, neurons in the guinea pig myenteric plexus were less sensitive than those in the submucous plexus [72] which may be related to the fact that mast cells are rarely present in the myenteric plexus layer under normal conditions. However, in the submucous layer there are numerous mast cells and it seems plausible that neurons in this area should be prepared to respond to a mast cell mediator cocktail.

The most important mast cell mediator is histamine. Since only mast cells and basophilic cells contain histamine in man and only a few basophile are present in the human mucosa, histamine can be used as a marker for mast cell degranulation. The pathophysiological relevance of histamine has been frequently shown in allergic and non-allergic diseases including gastrointestinal diseases such as IBD and IBS [18,38,64,74–78]. In the human intestine histamine influences a variety of gut functions including fluid and ion transport [79–81] which is partly nerve mediated [79]. Histamine directly excites human submucous neurons [82]. This effect was mediated by the activation of the four histamine receptor subtypes H1, H2; H3 and H4. The application of receptor specific agonists revealed receptor clustering on submucous neurons showing most frequently H1/H3 (29%), H2 (27%) and H1/H2/H3 (20%) clusters. Most striking was the identification of an excitatory H3 mediated component in humans submucous neurons while H3 receptors mediate suppression of fast synaptic transmission in the guinea-pig submucous plexus [82]. In rodents histamine had been demonstrated to act on presynaptic H3 receptors to suppress the release of acetylcholine and somatostatin from enteric neurons as well as the release of noradrenalin from sympathetic terminals [83–86]. The plasticity in histamine receptor expression in patients with food allergy and IBS, in particular an increase in H1 and H2 receptor mRNA levels, emphasizes the potential clinical benefit of drugs that act on histaminergic pathways [87]. Information on the effects of histamine on extrinsic sensory neurons of the gut derives exclusively from studies in rodents [4]. In rats H1 receptors have been

identified on extrinsic neurons in the jejunum [88]. Recently, it was shown that histamine or serotonin application to rat dorsal root ganglion cells with projections to the viscera increased the Ca^{2+} responses to a TRPV4 (transient receptor potential cation channel subfamily V member 4) agonist and enhanced the TRPV4 expression [89]. TRPV4 is known to be involved in visceral hypersensitivity.

Sensitization of extrinsic afferent neurons by mast cell mediators in particular histamine and proteases has been demonstrated in animal models. Similar mechanisms may also be operative in the human gut [90–92]. Application of an "inflammatory soup" composed of PGE_2, histamine, serotonin, ATP, adenosine and bradykinin increased the spiking activity of afferents nerves [91].

Another group of mast cells mediators comprises the prostaglandins (PGs) and leukotrienes (LTs) which are synthesized from the precursor arachidonic acid by cyclooxygenase and lipoxygenase enzymes, respectively. Among these substances PGD2 is the dominant prostanoid and LTC4, LTD4, and LTE4 are the most prevalent leukotrienes produced by human mast cells [19,93]. It was shown in rodents that each of these mediators strongly stimulate intestinal secretion [94]. These effects were partly mediated by direct actions on enteric neurons. Intracellular recordings in guinea pig submucous plexus revealed an activation of the neurons by all the mediators [95]. Whether similar mechanisms are active in humans is unclear. However, PGD2 receptors (DP) have been localized within the mucous-secreting goblet cells of the human colon [96]. Recently an inducible system for PGE2 generation in cultured human cord blood mast cells was detected and described [97]. Since PGE2 plays a major role in non-allergic diseases similar studies in human enteric mast cells would be interesting.

A variety of different cytokines, chemokines and growth factors has been identified in human mast cells (Table 1). Most of them are not stored preformed but synthesized de novo in active mast cells. There is evidence that IL-1β and TNFα, but not IFN-γ, IFN-α, IL-6 or IL-8 exhibit prosecretory effects in the human distal colon [98]. The effects were TTX insensitive but could be blocked by indomethacine. This indicates an additional effect of prostaglandins rather than an involvement of the ENS in this mechanism. In guinea-pig submucous and myenteric neurons IL-1β induced an indomethacine sensitive c-Fos expression [94] suggesting an indirect effect on the ENS which involves prostaglandins. Results from human submucous neurons demonstrated a direct excitatory action of IL-1β on enteric neurons [99]. Further knowledge on the influence of cytokines on enteric neurons derives from studies in laboratory animals. Frequently studied substances are IL-1β and IL-6. Both are reported to increase excitability in submucous and myenteric neurons and to mediate effects on cholinergic and non-cholinergic transmission [100–102]. IL-1β also sensitizes extrinsic visceral afferents of cats to histamine or excite them directly at higher doses [103].

It is generally believed and stated in many reviews that human intestinal mast cells do not release serotonin. This would be supported by our own results which show a consistent lack of serotonin immunoreactivity in human intestinal mast cells (Fig. 1). Also human isolated mast cells do not release serotonin in response to IgE receptor cross linking (personal communication Prof. Stephan Bischoff, University Hohenheim). However, there is no original paper that actually substantiates the assumption that human intestinal mast cells cannot release serotonin. There are two publications that demonstrate presence of serotonin in human intestinal mast cells. The first paper described the presence of serotonin immunoreactivity in about 30% of mast cells in normal tissue from patients with rectal carcinoma [49]. Their number is increased more than threefold in the colon of patients with UC. This study also showed an electron micrograph of a serotonin containing mast cell degranulating in the lumen of a gland. The second paper reported that cultured human mast cells derived from $CD34^+$ peripheral blood progenitors are able to release serotonin although the serotonin levels were much smaller than those released from mouse mast cells [104]. The same study also found that human mast cells express the serotonin synthesizing enzyme tryptophan hydroxylase. Thus the jury is still out on the ability or inability of mast cells to synthesize and release serotonin. In case it turns out that mast cells do under certain conditions or in response to a particular stimulus release serotonin, this serotonin may then act on nerves nearby. Human

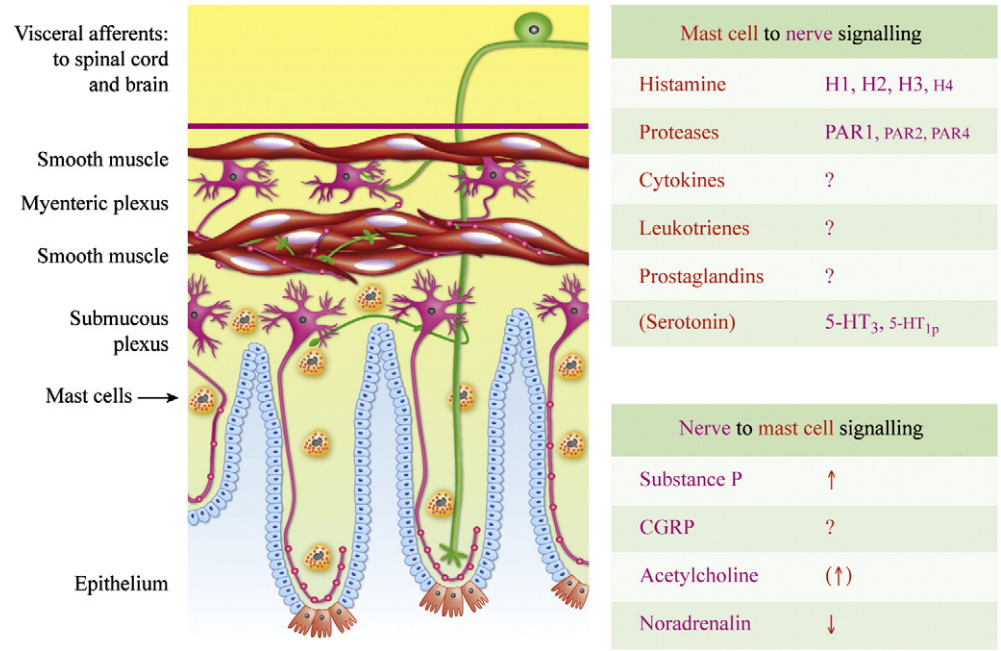

Fig. 2. Schematic illustration of mast cell nerve interactions in the human gut based on staining patterns such as those shown in Fig. 1 and functional data. The diagram takes into account the mast cell gradient along the gut wall with the highest density in the epithelial/subepithelial layer. Mast cell mediators excite enteric neurons through the receptors listed. Smaller fonts illustrate smaller contribution of the receptor. On the other hand, neurotransmitters released from enteric nerves or visceral afferents modulate mast cell mediator release (↑ increase; ↓ decrease).

submucous neurons would respond with a transient excitation mediated primarily by 5-HT_3 receptors [105].

Proteases, in particular the serine protease tryptase, are prominent mediators released from mast cells. Tryptase is present in almost all human mast cells, comprising up to 25% of their total proteins [106]. In patients with UC tryptase induces the production and release of inflammatory cytokines and chemokines [107] some of which may exert their effects through nerve pathways as outlined above. Proteases signal to nerves through proteinase-activated receptors (PARs) [108–110]. So far four cloned PAR receptors have been identified in humans. PAR1 and PAR3 are predominantly activated by thrombin, PAR2 is activated by trypsin and mast cell tryptase, PAR4 has equal affinity for thrombin and trypsin [111–113]. Guinea-pig ENS expresses PAR1, PAR2 and PAR4 which mediate activation of enteric neurons [114,115]. Recent studies focused on the role of neural PAR2 in various animal models. Thus PAR2 activation in mice increases intestinal permeability, which is mediated by SP and capsaicin-sensitive spinal afferent nerves [116]. In rats PAR2 activation evoked visceral hypersensitivity [117]. There are some noteworthy differences in the action of PAR activating peptides in the human ENS: PAR1 activation is the most important neural pathway; PAR4 activation occurs only in a minority of neurons while PAR2 activation is almost negligible [118]. The functional relevance of this effect was demonstrated by the finding that only PAR1 but not PAR2 activation leads to increased nerve-dependent secretion in human intestinal mucosa/submucosa preparations. A schematic illustration and summary of mast cell–nerve interactions in the human gut is given in Fig. 2.

7. Functional relevance of mast cell nerve interactions for translational neurogastro-enterology

The concentration of histamine and proteases is increased in supernatants from mucosal biopsies of IBS patients [74,75] and supernatants from stool of IBS and UC patients contain increased protease levels [119]. In both diseases an increased density of mucosal mast cells in close proximity to nerve endings [120], as well as an increased concentration of the mast cell products histamine and tryptase, and also certain cytokines and prostaglandins were found in the mucosa [40,64,77,120–124]. The increased concentration of mast cell mediators in the diseased gut may sensitize enteric neurons as well as visceral afferents. Thus mucosal biopsy supernatants from IBS patients activate human enteric neurons [75]. Histamine and in particular proteases play a major role in this activation which may explain alterations of gut functions in IBS patients. The same supernatants do also activate rat visceral afferents [74], an action that may contribute to visceral hypersensitivity. It is noteworthy that the mast cell stabilizer ketotifen improves the symptom score in IBS patients [78].

Likewise, mucosal biopsy supernatants from UC patients activate mouse DRG neurons innervating colon [125]. The key mediator here is TNFα. A possible TNFα contribution to the excitatory actions of IBS supernatants has not been tested. Likewise the contribution of histamine and proteases has not been tested for UC supernatants. It is therefore not possible to conclude at this stage on whether the underlying mechanisms responsible for the excitatory actions of IBS or UC supernatants are different.

8. Concluding remarks

There is clear evidence for functional mast cell to nerve signaling and nerve to mast cell signaling in the human intestine. While activation of mast cells cause mostly nerve sensitization nerves can activate or inhibit mast cell mediator release. It is suggested that these interactions play an important role in symptom generation or even pathogenesis of functional and inflammatory bowel disorders.

References

[1] G.E. Boeckxstaens, Neuroimmune interaction in the gut: from bench to bedside, Verh. K. Acad. Geneeskd. Belg. 68 (2006) 329–355.
[2] A.D. Kraneveld, A. Rijnierse, F.P. Nijkamp, J. Garssen, Neuro-immune interactions in inflammatory bowel disease and irritable bowel syndrome: future therapeutic targets, Eur. J. Pharmacol. 585 (2008) 361–374.
[3] A. Rijnierse, F.P. Nijkamp, A.D. Kraneveld, Mast cells and nerves tickle in the tummy: implications for inflammatory bowel disease and irritable bowel syndrome, Pharmacol. Ther. 116 (2007) 207–235.
[4] L. Van Nassauw, D. Adriaensen, J.P. Timmermans, The bidirectional communication between neurons and mast cells within the gastrointestinal tract, Auton. Neurosci. 133 (2007) 91–103.
[5] J.D. Wood, Enteric neuroimmunophysiology and pathophysiology, Gastroenterology 127 (2004) 635–657.
[6] H.J. Cooke, Role of the "little brain" in the gut in water and electrolyte homeostasis, FASEB J. 3 (1989) 127–138.
[7] M. Costa, S.J. Brookes, G.W. Hennig, Anatomy and physiology of the enteric nervous system, Gut 47 (2000) iv15–iv19.
[8] J.B. Furness, Types of neurons in the enteric nervous system, J. Auton. Nerv. Syst. 81 (2000) 87–96.
[9] P. Holzer, T. Michl, M. Danzer, M. Jocic, R. Schicho, I.T. Lippe, Surveillance of the gastrointestinal mucosa by sensory neurons, J. Physiol. Pharmacol. 52 (2001) 505–521.
[10] M. Schemann, M. Neunlist, The human enteric nervous system, Neurogastroenterol. Motil. 16 (Suppl. 1) (2004) 55–59.
[11] J. Schneider, E.C. Jehle, M.J. Starlinger, M. Neunlist, K. Michel, S. Hoppe, M. Schemann, Neurotransmitter coding of enteric neurones in the submucous plexus is changed in non-inflamed rectum of patients with Crohn's disease, Neurogastroenterol. Motil. 13 (2001) 255–264.
[12] M. Anlauf, M.K. Schafer, L. Eiden, E. Weihe, Chemical coding of the human gastrointestinal nervous system: cholinergic, VIPergic, and catecholaminergic phenotypes, J. Comp. Neurol. 459 (2003) 90–111.
[13] M. Schemann, K. Michel, S. Peters, S.C. Bischoff, M. Neunlist, Cutting-edge technology. III. Imaging and the gastrointestinal tract: mapping the human enteric nervous system, Am. J. Physiol. Gastrointest. Liver Physiol. 282 (2002) G919–G925.
[14] S.C. Bischoff, J. Wedemeyer, A. Herrmann, P.N. Meier, C. Trautwein, Y. Cetin, H. Maschek, M. Stolte, M. Gebel, M.P. Manns, Quantitative assessment of intestinal eosinophils and mast cells in inflammatory bowel disease, Histopathology 28 (1996) 1–13.
[15] M.F. Gurish, J.A. Boyce, Mast cells: ontogeny, homing, and recruitment of a unique innate effector cell, J. Allergy Clin. Immunol. 117 (2006) 1285–1291.
[16] A.A. Irani, N.M. Schechter, S.S. Craig, G. DeBlois, L.B. Schwartz, Two types of human mast cells that have distinct neutral protease compositions, Proc. Natl Acad. Sci. U. S. A. 83 (1986) 4464–4468.
[17] M.A. Lowman, P.H. Rees, R.C. Benyon, M.K. Church, Human mast cell heterogeneity: histamine release from mast cells dispersed from skin, lung, adenoids, tonsils, and colon in response to IgE-dependent and nonimmunologic stimuli, J. Allergy Clin. Immunol. 81 (1988) 590–597.
[18] S.C. Bischoff, Role of mast cells in allergic and non-allergic immune responses: comparison of human and murine data, Nat. Rev. Immunol. 7 (2007) 93–104.
[19] S.C. Bischoff, Physiological and pathophysiological functions of intestinal mast cells, Semin. Immunopathol. 31 (2009) 185–205.
[20] M. Kulka, N. Fukuishi, M. Rottem, Y.A. Mekori, D.D. Metcalfe, Mast cells, which interact with *Escherichia coli*, up-regulate genes associated with innate immunity and become less responsive to Fc(epsilon)RI-mediated activation, J. Leukoc. Biol. 79 (2006) 339–350.
[21] I. Leal-Berumen, D.P. Snider, C. Barajas-Lopez, J.S. Marshall, Cholera toxin increases IL-6 synthesis and decreases TNF-alpha production by rat peritoneal mast cells, J. Immunol. 156 (1996) 316–321.
[22] R. Malaviya, Z. Gao, K. Thankavel, P.A. van der Merwe, S.N. Abraham, The mast cell tumor necrosis factor alpha response to FimH-expressing *Escherichia coli* is mediated by the glycosylphosphatidylinositol-anchored molecule CD48, Proc. Natl Acad. Sci. U. S. A. 96 (1999) 8110–8115.
[23] G. Sellge, S. Laffer, C. Mierke, S. Vrtala, M.W. Hoffmann, J. Klempnauer, M.P. Manns, R. Valenta, S.C. Bischoff, Development of an in vitro system for the study of allergens and allergen-specific immunoglobulin E and immunoglobulin G: Fcepsilon receptor I supercross-linking is a possible new mechanism of immunoglobulin G-dependent enhancement of type I allergic reactions, Clin. Exp. Allergy 35 (2005) 774–781.
[24] S.C. Bischoff, S. Schwengberg, A. Lorentz, M.P. Manns, H. Bektas, H. Sann, F. Levi-Schaffer, F. Shanahan, M. Schemann, Substance P and other neuropeptides do not induce mediator release in isolated human intestinal mast cells, Neurogastroenterol. Motil. 16 (2004) 185–193.
[25] S. Guhl, H.H. Lee, M. Babina, B.M. Henz, T. Zuberbier, Evidence for a restricted rather than generalized stimulatory response of skin-derived human mast cells to substance P, J. Neuroimmunol. 163 (2005) 92–101.
[26] H.P. van der Kleij, D. Ma, F.A. Redegeld, A.D. Kraneveld, F.P. Nijkamp, J. Bienenstock, Functional expression of neurokinin 1 receptors on mast cells induced by IL-4 and stem cell factor, J. Immunol. 171 (2003) 2074–2079.
[27] S.C. Bischoff, G. Sellge, A. Lorentz, W. Sebald, R. Raab, M.P. Manns, IL-4 enhances proliferation and mediator release in mature human mast cells, Proc. Natl Acad. Sci. U. S. A. 96 (1999) 8080–8085.
[28] A. Lorentz, S. Schwengberg, G. Sellge, M.P. Manns, S.C. Bischoff, Human intestinal mast cells are capable of producing different cytokine profiles: role of IgE receptor cross-linking and IL-4, J. Immunol. 164 (2000) 43–48.

[29] A. Lorentz, M. Wilke, G. Sellge, H. Worthmann, J. Klempnauer, M.P. Manns, S.C. Bischoff, IL-4-induced priming of human intestinal mast cells for enhanced survival and Th2 cytokine generation is reversible and associated with increased activity of ERK1/2 and c-Fos, J. Immunol. 174 (2005) 6751–6756.
[30] K. Matsuda, A.M. Piliponsky, M. Iikura, S. Nakae, E.W. Wang, S.M. Dutta, T. Kawakami, M. Tsai, S.J. Galli, Monomeric IgE enhances human mast cell chemokine production: IL-4 augments and dexamethasone suppresses the response, J. Allergy Clin. Immunol. 116 (2005) 1357–1363.
[31] D. Miyazaki, T. Nakamura, M. Toda, K.W. Cheung-Chau, R.M. Richardson, S.J. Ono, Macrophage inflammatory protein-1alpha as a costimulatory signal for mast cell-mediated immediate hypersensitivity reactions, J. Clin. Invest. 115 (2005) 434–442.
[32] T. Gebhardt, A. Lorentz, F. Detmer, C. Trautwein, H. Bektas, M.P. Manns, S.C. Bischoff, Growth, phenotype, and function of human intestinal mast cells are tightly regulated by transforming growth factor beta 1, Gut 54 (2005) 928–934.
[33] B. Royer, S. Varadaradjalou, P. Saas, J.J. Guillosson, J.P. Kantelip, M. Arock, Inhibition of IgE-induced activation of human mast cells by IL-10, Clin. Exp. Allergy 31 (2001) 694–704.
[34] R.H. Stead, M.F. Dixon, N.H. Bramwell, R.H. Riddell, J. Bienenstock, Mast cells are closely apposed to nerves in the human gastrointestinal mucosa, Gastroenterology 97 (1989) 575–585.
[35] R.H. Stead, Innervation of mucosal immune cells in the gastrointestinal tract, Reg. Immunol. 4 (1992) 91–99.
[36] J. Bienenstock, G. MacQueen, P. Sestini, J.S. Marshall, R.H. Stead, M.H. Perdue, Mast cell/nerve interactions in vitro and in vivo, Am. Rev. Respir. Dis. 143 (1991) S55–S58.
[37] G.D. Wang, X. Wang, Y. Xia, S. Liu, M.H. Qu, W. Ren, J.D. Wood, Stimulation of spinal afferents evokes slowly-activating excitatory responses in enteric neurons in parallel with release of mast cell proteases in guinea pig ileum and colon, Gastroenterology 136 (2009) A107.
[38] M. Raithel, H.T. Schneider, E.G. Hahn, Effect of substance P on histamine secretion from gut mucosa in inflammatory bowel disease, Scand. J. Gastroenterol. 34 (1999) 496–503.
[39] C.A. Maggi, The effects of tachykinins on inflammatory and immune cells, Regul. Pept. 70 (1997) 75–90.
[40] W.Z. Dong, D.W. Zou, Z.S. Li, X.P. Zou, A.Y. Zhu, G.M. Xu, N. Yin, Y.F. Gong, Z.X. Sun, X.H. Man, Study of visceral hypersensitivity in irritable bowel syndrome, Chin. J. Dig. Dis. 5 (2004) 103–109.
[41] X. Pang, W. Boucher, G. Triadafilopoulos, G.R. Sant, T.C. Theoharides, Mast cell and substance P-positive nerve involvement in a patient with both irritable bowel syndrome and interstitial cystitis, Urology 47 (1996) 436–438.
[42] A. Akbar, Y. Yiangou, P. Facer, J.R. Walters, P. Anand, S. Ghosh, Increased capsaicin receptor TRPV1-expressing sensory fibres in irritable bowel syndrome and their correlation with abdominal pain, Gut 57 (2008) 923–929.
[43] I. Castagliuolo, J.T. LaMont, R. Letourneau, C. Kelly, J.C. O'Keane, A. Jaffer, T.C. Theoharides, C. Pothoulakis, Neuronal involvement in the intestinal effects of Clostridium difficile toxin A and Vibrio cholerae enterotoxin in rat ileum, Gastroenterology 107 (1994) 657–665.
[44] I. Castagliuolo, M. Riegler, A. Pasha, S. Nikulasson, B. Lu, C. Gerard, N.P. Gerard, C. Pothoulakis, Neurokinin-1 (NK-1) receptor is required in Clostridium difficile-induced enteritis, J. Clin. Invest. 101 (1998) 1547–1550.
[45] C. Pothoulakis, I. Castagliuolo, J.T. LaMont, A. Jaffer, J.C. O'Keane, R.M. Snider, S.E. Leeman, CP-96,345, a substance P antagonist, inhibits rat intestinal responses to Clostridium difficile toxin A but not cholera toxin, Proc. Natl Acad. Sci. U. S. A. 91 (1994) 947–951.
[46] B.K. Wershil, I. Castagliuolo, C. Pothoulakis, Direct evidence of mast cell involvement in Clostridium difficile toxin A-induced enteritis in mice, Gastroenterology 114 (1998) 956–964.
[47] A. Rijnierse, K.M. van Zijl, A.S. Koster, F.P. Nijkamp, A.D. Kraneveld, Beneficial effect of tachykinin NK1 receptor antagonism in the development of hapten-induced colitis in mice, Eur. J. Pharmacol. 548 (2006) 150–157.
[48] G. Barbara, V. Stanghellini, R. De Giorgio, R. Corinaldesi, Functional gastrointestinal disorders and mast cells: implications for therapy, Neurogastroenterol. Motil. 18 (2006) 6–17.
[49] I.I. Stoyanova, M.V. Gulubova, Mast cells and inflammatory mediators in chronic ulcerative colitis, Acta Histochem. 104 (2002) 185–192.
[50] K.J. Gross, C. Pothoulakis, Role of neuropeptides in inflammatory bowel disease, Inflamm. Bowel Dis. 13 (2007) 918–932.
[51] S.E. Lakhan, A. Kirchgessner, Neuroinflammation in inflammatory bowel disease, J. Neuroinflammation 7 (2010) 37.
[52] A. Belai, P.B. Boulos, T. Robson, G. Burnstock, Neurochemical coding in the small intestine of patients with Crohn's disease, Gut 40 (1997) 767–774.
[53] F. De Jonge, A. De Laet, L. Van Nassauw, J.K. Brown, H.R. Miller, P.P. van Bogaert, J.P. Timmermans, A.B. Kroese, In vitro activation of murine DRG neurons by CGRP-mediated mucosal mast cell degranulation, Am. J. Physiol. Gastrointest. Liver Physiol. 287 (2004) G178–G191.
[54] F.K. Renold, P. Dazin, E.J. Goetzl, D.G. Payan, Interleukin-3 modulation of mouse bone marrow derived mast cell receptors for somatostatin, J. Neurosci. Res. 18 (1987) 195–202.
[55] R.H. Stead, E.C. Colley, B.X. Wang, E. Partosoedarso, J.H. Lin, A. Stanisz, K. Hillsley, Vagal influences over mast cells, Auton. Neurosci. Basic Clin. 125 (2006) 53–61.
[56] J. Santos, E. Saperas, C. Nogueiras, M. Mourelle, M. Antolin, A. Cadahia, J.R. Malagelada, Release of mast cell mediators into the jejunum by cold pain stress in humans, Gastroenterology 114 (1998) 640–648.
[57] A.D. Befus, N. Dyck, R. Goodacre, J. Bienenstock, Mast cells from the human intestinal lamina propria. Isolation, histochemical subtypes, and functional characterization, J. Immunol. 138 (1987) 2604–2610.
[58] M. Kaliner, Human lung tissue and anaphylaxis. I. The role of cyclic GMP as a modulator of the immunologically induced secretory process, J. Allergy Clin. Immunol. 60 (1977) 204–211.
[59] T. Gebhardt, R. Gerhard, S. Bedoui, V.J. Erpenbeck, M.W. Hoffmann, M.P. Manns, S.C. Bischoff, beta2-Adrenoceptor-mediated suppression of human intestinal mast cell functions is caused by disruption of filamentous actin dynamics, Eur. J. Immunol. 35 (2005) 1124–1132.
[60] T. Bani-Sacchi, M. Barattini, S. Bianchi, P. Blandina, S. Brunelleschi, R. Fantozzi, P.F. Mannaioni, E. Masini, The release of histamine by parasympathetic stimulation in guinea-pig auricle and rat ileum, J. Physiol. 371 (1986) 29–43.
[61] M. Kaliner, R.P. Orange, K.F. Austen, Immunological release of histamine and slow reacting substance of anaphylaxis from human lung, J. Exp. Med. 136 (1972) 556–567.
[62] Y. Tache, M.H. Perdue, Role of peripheral CRF signalling pathways in stress-related alterations of gut motility and mucosal function, Neurogastroenterol. Motil. 16 (Suppl. 1) (2004) 137–142.
[63] J. Cao, N. Papadopoulou, D. Kempuraj, W.S. Boucher, K. Sugimoto, C.L. Cetrulo, T.C. Theoharides, Human mast cells express corticotropin-releasing hormone (CRH) receptors and CRH leads to selective secretion of vascular endothelial growth factor, J. Immunol. 174 (2005) 7665–7675.
[64] S.H. He, Key role of mast cells and their major secretory products in inflammatory bowel disease, World J. Gastroenterol. 10 (2004) 309–318.
[65] T. Frieling, J.M. Palmer, H.J. Cooke, J.D. Wood, Neuroimmune communication in the submucous plexus of guinea pig colon after infection with *Trichinella spiralis*, Gastroenterology 107 (1994) 1602–1609.
[66] T. Frieling, H.J. Cooke, J.D. Wood, Neuroimmune communication in the submucous plexus of guinea pig colon after sensitization to milk antigen, Am. J. Physiol. 267 (1994) G1087–G1093.
[67] N.H. Javed, Y.Z. Wang, H.J. Cooke, Neuroimmune interactions: role for cholinergic neurons in intestinal anaphylaxis, Am. J. Physiol. 263 (1992) G847–G852.
[68] S. Liu, H.Z. Hu, N. Gao, C. Gao, G. Wang, X. Wang, O.C. Peck, G. Kim, X. Gao, Y. Xia, J.D. Wood, Neuroimmune interactions in guinea pig stomach and small intestine, Am. J. Physiol. Gastrointest. Liver Physiol. 284 (2003) G154–G164.
[69] Y.Z. Wang, J.M. Palmer, H.J. Cooke, Neuroimmune regulation of colonic secretion in guinea pigs, Am. J. Physiol. 260 (1991) G307–G314.
[70] M.S. Barnette, M. Grous, Characterization of the antigen-induced contraction of colonic smooth muscle from sensitized guinea pigs, Am. J. Physiol. 262 (1992) G144–G149.
[71] P. Molkhou, C. Dupont, Ketotifen in prevention and therapy of food allergy, Ann. Allergy 59 (1987) 187–193.
[72] M. Schemann, K. Michel, M. Ceregrzyn, F. Zeller, S. Seidl, S.C. Bischoff, Human mast cell mediator cocktail excites neurons in human and guinea-pig enteric nervous system, Neurogastroenterol. Motil. 17 (2005) 281–289.
[73] D.R. Linden, K.A. Sharkey, G.M. Mawe, Enhanced excitability of myenteric AH neurones in the inflamed guinea-pig distal colon, J. Physiol. 547 (2003) 589–601.
[74] G. Barbara, B. Wang, V. Stanghellini, R. De Giorgio, C. Cremon, G. Di Nardo, M. Trevisani, B. Campi, P. Geppetti, M. Tonini, N.W. Bunnett, D. Grundy, R. Corinaldesi, Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome, Gastroenterology 132 (2007) 26–37.
[75] S. Buhner, Q. Li, S. Vignali, G. Barbara, R. De Giorgio, V. Stanghellini, C. Cremon, F. Zeller, R. Langer, H. Daniel, K. Michel, M. Schemann, Activation of human enteric neurons by supernatants of colonic biopsy specimens from patients with irritable bowel syndrome, Gastroenterology 137 (2009) 1425–1434.
[76] C.C. Fox, L.M. Lichtenstein, J.K. Roche, Intestinal mast cell responses in idiopathic inflammatory bowel disease. Histamine release from human intestinal mast cells in response to gut epithelial proteins, Dig. Dis. Sci. 38 (1993) 1105–1112.
[77] M. Guilarte, J. Santos, I. de Torres, C. Alonso, M. Vicario, L. Ramos, C. Martinez, F. Casellas, E. Saperas, J.R. Malagelada, Diarrhoea-predominant IBS patients show mast cell activation and hyperplasia in the jejunum, Gut 56 (2007) 203–209.
[78] T.K. Klooker, B. Braak, K.E. Koopman, O. Welting, M.M. Wouters, H.S. van der, M. Schemann, S.C. Bischoff, R.M. van den Wijngaard, G.E. Boeckxstaens, The mast cell stabiliser ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome, Gut 59 (2010) 1213–1221.
[79] S.E. Crowe, M.H. Perdue, Anti-immunoglobulin E-stimulated ion transport in human large and small intestine, Gastroenterology 105 (1993) 764–772.
[80] S.J. Keely, W.A. Stack, D.P. O'Donoghue, A.W. Baird, Regulation of ion transport by histamine in human colon, Eur. J. Pharmacol. 279 (1995) 203–209.
[81] W.A. Stack, S.J. Keely, D.P. O'Donoghue, A.W. Baird, Immune regulation of human colonic electrolyte transport in vitro, Gut 36 (1995) 395–400.
[82] E. Breunig, K. Michel, F. Zeller, S. Seidl, C.W. Weyhern, M. Schemann, Histamine excites neurones in the human submucous plexus through activation of H1, H2, H3 and H4 receptors, J. Physiol. 583 (2007) 731–742.
[83] T. Frieling, H.J. Cooke, J.D. Wood, Histamine receptors on submucous neurons in guinea pig colon, Am. J. Physiol. 264 (1993) G74–G80.
[84] S. Liu, Y. Xia, Hz Hu, J. Ren, C. Gao, J.D. Wood, Histamine H3 receptor-mediated suppression of inhibitory synaptic transmission in the submucous plexus of guinea-pig small intestine, Eur. J. Pharmacol. 397 (2000) 49–54.
[85] P.R. Nemeth, C.A. Ort, J.D. Wood, Intracellular study of effects of histamine on electrical behaviour of myenteric neurones in guinea-pig small intestine, J. Physiol. (Lond.) 355 (1984) 411–425.
[86] K. Tamura, J.M. Palmer, J.D. Wood, Presynaptic inhibition produced by histamine at nicotinic synapses in enteric ganglia, Neuroscience 25 (1988) 171–179.
[87] L.E. Sander, A. Lorentz, G. Sellge, M. Coeffier, M. Neipp, T. Veres, T. Frieling, P.N. Meier, M.P. Manns, S.C. Bischoff, Selective expression of histamine receptors H1R, H2R, and H4R, but not H3R, in the human intestinal tract, Gut 55 (2006) 498–504.

[88] M.E. Kreis, W. Jiang, A.J. Kirkup, D. Grundy, Cosensitivity of vagal mucosal afferents to histamine and 5-HT in the rat jejunum, Am. J. Physiol. Gastrointest. Liver Physiol. 283 (2002) G612–G617.
[89] N. Cenac, C. Altier, J.P. Motta, E. d'Aldebert, S. Galeano, G.W. Zamponi, N. Vergnolle, Potentiation of TRPV4 signalling by histamine and serotonin: an important mechanism for visceral hypersensitivity, Gut 59 (2010) 481–488.
[90] W. Jiang, I.J. Adam, P. Kitsanta, J. Tiernan, C. Hill, A. Shorthouse, D. Grundy, 'First-in-man': characterising the mechanosensitivity of human colonic afferents, Gut 60 (2011) 281–282.
[91] M. Peiris, D.C. Bulmer, M.D. Baker, G. Boundouki, S. Sinha, A. Hobson, K. Lee, Q. Aziz, C.H. Knowles, Human visceral afferent recordings: preliminary report, Gut 60 (2011) 204–208.
[92] M. Schemann, Recording from human gut tissue: a major step towards more efficient drug development? Gut 60 (2011) 151–152.
[93] H. Vliagoftis, A.D. Befus, Mast cells at mucosal frontiers, Curr. Mol. Med. 5 (2005) 573–589.
[94] K.A. Sharkey, A.B. Kroese, Consequences of intestinal inflammation on the enteric nervous system: neuronal activation induced by inflammatory mediators, Anat. Rec. 262 (2001) 79–90.
[95] T. Frieling, C. Rupprecht, G. Dobreva, M. Schemann, Differential effects of inflammatory mediators on ion secretion in the guinea-pig colon, Comp. Biochem. Physiol. A Physiol. 118 (1997) 341–343.
[96] D.H. Wright, A.W. Ford-Hutchinson, K. Chadee, K.M. Metters, The human prostanoid DP receptor stimulates mucin secretion in LS174T cells, Br. J. Pharmacol. 131 (2000) 1537–1545.
[97] C. Feng, E.M. Beller, S. Bagga, J.A. Boyce, Human mast cells express multiple EP receptors for prostaglandin E2 that differentially modulate activation responses, Blood 107 (2006) 3243–3250.
[98] H. Bode, H. Schmitz, M. Fromm, P. Scholz, E.O. Riecken, J.D. Schulzke, IL-1beta and TNF-alpha, but not IFN-alpha, IFN-gamma, IL-6 or IL-8, are secretory mediators in human distal colon, Cytokine 10 (1998) 457–465.
[99] M. Neunlist, J. Barouk, K. Michel, I. Just, T. Oreshkova, M. Schemann, J.P. Galmiche, Toxin B of Clostridium difficile activates human VIP submucosal neurons, in part via an IL-1beta-dependent pathway, Am. J. Physiol. Gastrointest. Liver Physiol. 285 (2003) G1049–G1055.
[100] A. Kelles, J. Janssens, J. Tack, IL-1beta and IL-6 excite neurones and suppress cholinergic neurotransmission in the myenteric plexus of the guinea pig, Neurogastroenterol. Motil. 12 (2000) 531–538.
[101] A. Kelles, J. Janssens, J. Tack, Electrical behaviour of interleukin-1 beta (IL-1 beta) and prostaglandin-E2 (PGE2) on colonic myenteric neurones, Neurogastroenterol. Motil. 14 (2002) 321–330.
[102] Y. Xia, H.Z. Hu, S. Liu, J. Ren, D.H. Zafirov, J.D. Wood, IL-1beta and IL-6 excite neurons and suppress nicotinic and noradrenergic neurotransmission in guinea pig enteric nervous system, J. Clin. Invest. 103 (1999) 1309–1316.
[103] L.W. Fu, J.C. Longhurst, Interleukin-1beta sensitizes abdominal visceral afferents of cats to ischaemia and histamine, J. Physiol. 521 (Pt 1) (1999) 249–260.
[104] N.M. Kushnir-Sukhov, J.M. Brown, Y. Wu, A. Kirshenbaum, D.D. Metcalfe, Human mast cells are capable of serotonin synthesis and release, J. Allergy Clin. Immunol. 119 (2007) 498–499.
[105] K. Michel, F. Zeller, R. Langer, H. Nekarda, D. Kruger, T.J. Dover, C.A. Brady, N.M. Barnes, M. Schemann, Serotonin excites neurons in the human submucous plexus via 5-HT3 receptors, Gastroenterology 128 (2005) 1317–1326.
[106] L.B. Schwartz, R.A. Lewis, K.F. Austen, Tryptase from human pulmonary mast cells. Purification and characterization, J. Biol. Chem. 256 (1981) 11939–11943.
[107] J.A. Kim, S.C. Choi, K.J. Yun, D.K. Kim, M.K. Han, G.S. Seo, J.J. Yeom, T.H. Kim, Y.H. Nah, Y.M. Lee, Expression of protease-activated receptor 2 in ulcerative colitis, Inflamm. Bowel Dis. 9 (2003) 224–229.
[108] O. Dery, C.U. Corvera, M. Steinhoff, N.W. Bunnett, Proteinase-activated receptors: novel mechanisms of signaling by serine proteases, Am. J. Physiol. 274 (1998) C1429–C1452.
[109] S.R. Macfarlane, M.J. Seatter, T. Kanke, G.D. Hunter, R. Plevin, Proteinase-activated receptors, Pharmacol. Rev. 53 (2001) 245–282.
[110] N. Vergnolle, J.L. Wallace, N.W. Bunnett, M.D. Hollenberg, Protease-activated receptors in inflammation, neuronal signaling and pain, Trends Pharmacol. Sci. 22 (2001) 146–152.
[111] S.K. Bohm, W. Kong, D. Bromme, S.P. Smeekens, D.C. Anderson, A. Connolly, M. Kahn, N.A. Nelken, S.R. Coughlin, D.G. Payan, N.W. Bunnett, Molecular cloning, expression and potential functions of the human proteinase-activated receptor-2, Biochem. J. 314 (1996) 1009–1016.
[112] H. Ishihara, A.J. Connolly, D. Zeng, M.L. Kahn, Y.W. Zheng, C. Timmons, T. Tram, S.R. Coughlin, Protease-activated receptor 3 is a second thrombin receptor in humans, Nature 386 (1997) 502–506.
[113] W.F. Xu, H. Andersen, T.E. Whitmore, S.R. Presnell, D.P. Yee, A. Ching, T. Gilbert, E.W. Davie, D.C. Foster, Cloning and characterization of human protease-activated receptor 4, Proc. Natl Acad. Sci. U. S. A. 95 (1998) 6642–6646.
[114] C. Gao, S. Liu, H.Z. Hu, N. Gao, G.Y. Kim, Y. Xia, J.D. Wood, Serine proteases excite myenteric neurons through protease-activated receptors in guinea pig small intestine, Gastroenterology 123 (2002) 1554–1564.
[115] D.E. Reed, C. Barajas-Lopez, G. Cottrell, S. Velazquez-Rocha, O. Dery, E.F. Grady, N.W. Bunnett, S.J. Vanner, Mast cell tryptase and proteinase-activated receptor 2 induce hyperexcitability of guinea-pig submucosal neurons, J. Physiol. 547 (2003) 531–542.
[116] N. Cenac, R. Garcia-Villar, L. Ferrier, M. Larauche, N. Vergnolle, N.W. Bunnett, A.M. Coelho, J. Fioramonti, L. Bueno, Proteinase-activated receptor-2-induced colonic inflammation in mice: possible involvement of afferent neurons, nitric oxide, and paracellular permeability, J. Immunol. 170 (2003) 4296–4300.
[117] A.M. Coelho, N. Vergnolle, B. Guiard, J. Fioramonti, L. Bueno, Proteinases and proteinase-activated receptor 2: a possible role to promote visceral hyperalgesia in rats, Gastroenterology 122 (2002) 1035–1047.
[118] K. Mueller, K. Michel, D. Krueger, I.E. Demir, G.O. Ceyhan, F. Zeller, M.E. Kreis, M. Schemann, PAR-1 and PAR-2 receptor mediated actions in the human intestine, Neurogastroenterol. Motil. 22 (2010) 16.
[119] A. Annahazi, K. Gecse, M. Dabek, A. Ait-Belgnaoui, A. Rosztoczy, R. Roka, T. Molnar, V. Theodorou, T. Wittmann, L. Bueno, H. Eutamene, Fecal proteases from diarrheic-IBS and ulcerative colitis patients exert opposite effect on visceral sensitivity in mice, Pain 144 (2009) 209–217.
[120] G. Barbara, V. Stanghellini, R. De Giorgio, C. Cremon, G.S. Cottrell, D. Santini, G. Pasquinelli, A.M. Morselli-Labate, E.F. Grady, N.W. Bunnett, S.M. Collins, R. Corinaldesi, Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome, Gastroenterology 126 (2004) 693–702.
[121] K.A. Gwee, S.M. Collins, N.W. Read, A. Rajnakova, Y. Deng, J.C. Graham, M.W. McKendrick, S.M. Moochhala, Increased rectal mucosal expression of interleukin 1beta in recently acquired post-infectious irritable bowel syndrome, Gut 52 (2003) 523–526.
[122] J. Macsharry, L. O'Mahony, A. Fanning, E. Bairead, G. Sherlock, J. Tiesman, A. Fulmer, B. Kiely, T.G. Dinan, F. Shanahan, E.M. Quigley, Mucosal cytokine imbalance in irritable bowel syndrome, Scand. J. Gastroenterol. 43 (2008) 1467–1476.
[123] M. O'Sullivan, N. Clayton, N.P. Breslin, I. Harman, C. Bountra, A. McLaren, C.A. O'Morain, Increased mast cells in the irritable bowel syndrome, Neurogastroenterol. Motil. 12 (2000) 449–457.
[124] J.H. Park, P.L. Rhee, H.S. Kim, J.H. Lee, Y.H. Kim, J.J. Kim, J.C. Rhee, Mucosal mast cell counts correlate with visceral hypersensitivity in patients with diarrhea predominant irritable bowel syndrome, J. Gastroenterol. Hepatol. 21 (2006) 71–78.
[125] C. Ibeakanma, S. Vanner, TNFalpha is a key mediator of the pronociceptive effects of mucosal supernatant from human ulcerative colitis on colonic DRG neurons, Gut 59 (2010) 612–621.
[126] P. Bradding, I.H. Feather, S. Wilson, P.G. Bardin, C.H. Heusser, S.T. Holgate, P.H. Howarth, Immunolocalization of cytokines in the nasal-mucosa of normal and perennial rhinitic subjects — the mast-cell as a source of Il-4, Il-5, and Il-6 in human allergic mucosal inflammation, J. Immunol. 151 (1993) 3853–3865.
[127] S.J. Galli, S. Nakae, M. Tsai, Mast cells in the development of adaptive immune responses, Nat. Immunol. 6 (2005) 135–142.
[128] G. Nilsson, K. Forsberg-Nilsson, Z. Xiang, F. Hallbook, K. Nilsson, D.D. Metcalfe, Human mast cells express functional TrkA and are a source of nerve growth factor, Eur. J. Immunol. 27 (1997) 2295–2301.