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Role of visceral afferent neurons in mucosal inflammation and defence

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Summary

The maintenance of gastrointestinal mucosal integrity depends on the rapid alarm of protective mechanisms in the face of pending injury. Two populations of extrinsic primary afferent neurons, vagal and spinal, subserve this goal through different mechanisms. These sensory neurons react to gastrointestinal insults by triggering protective autonomic reflexes including the so-called cholinergic anti-inflammatory reflex. Spinal afferents, in addition, can initiate protective tissue reactions at the site of assault through release of calcitonin gene-related peptide from their peripheral endings. The protective responses triggered by sensory neurons comprise alterations in gastrointestinal blood flow, secretion and motility as well as modifications of immune function. This article focusses on significant advances that during the past couple of years have been made in identifying molecular nocisensors on afferent neurons and in dissecting the signalling mechanisms whereby afferent neurons govern inflammatory processes in the gut.

Keywords

Acid-sensing ion channel-3 (ASIC3); calcitonin gene-related peptide (CGRP); cholinergic anti-inflammatory reflex; gastroduodenal bicarbonate secretion; gastrointestinal blood flow; gastrointestinal immune system; primary afferent neurons; transient receptor potential vanilloid 1 (TRPV1) ion channel

Introduction

The physiological role of the gastrointestinal (GI) tract is not only to take up and digest food and absorb nutrients and water, but also to sort out and eliminate harmful and useless material. These seemingly conflicting tasks require a molecular analysis of the luminal contents and the functional status of the GI tract, so that the appropriate effector programmes can be selected [1]. To this end, the digestive system is endowed with an elaborate network of surveillance systems among which sensory neurons play a particular role. Thus, the gut is supplied by intrinsic sensory neurons of the enteric nerve plexuses as well as extrinsic spinal and vagal afferent neurons which are in close contact with two important non-neural surveillance systems in the mucosa: endocrine and immune cells [1].

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With these connections and their sensory modalities, GI sensory neurons are able to recognize subtle changes in the chemical and physical environment within the lumen, interstitial space, vasculature and muscle of the gut.

Sensory neurons subserve homeostasis and protection from adverse conditions through several mechanisms. These include (i) sensation of pain, alterations in (ii) emotion, affect and cognition, induction of (iii) autonomic reflexes and (iv) neuroendocrine responses, and initiation of (v) protective tissue reactions at the site of assault (Figure 1). Within the gut, the protective mechanisms triggered by sensory neurons comprise alterations in blood flow, secretion and motility and modifications of immune function. Work in the past decade has identified a phenomenal variety of molecular sensors that are expressed by primary afferent neurons and enable them to carry out their surveillance tasks [2]. This gain of knowledge has considerably advanced the understanding of both the physiology and pharmacology of afferent neurons in maintaining homeostasis of the GI mucosa in the face of challenge and injury. The current article highlights some of the most important advances that have been made in this field during the past two years.

Coordinated protection of the oesophago-gastro-duodenal region

Despite its essential role in digestion, gastric acid is a constant threat to the integrity of the mucosa in the stomach and the adjacent oesophageal and duodenal regions. Effective protection from the autoaggressive potential of acid is provided by mucosal defence mechanisms and appropriate compartmentalisation of the oesophago-gastro-duodenal region (Figure 2). The latter strategy is to prevent the escape of injurious concentrations of acid from the stomach, the mucosa of which is most resistant to intrusion by H^+. Both the lower oesophageal sphincter (LOS) and the pyloric sphincter are under the control of neural reflexes involving acid-sensitive neurons. The tone of these sphincters is adjusted such that the levels of acid present in the oesophagus, stomach and duodenum are balanced with the mucosal defence mechanisms in these compartments [3].

The pyloric sphincter controls gastric emptying and ensures that the acidified gastric contents are delivered to the duodenum at a rate that enables this most proximal region of the small intestine to cope with the imposed acid load [3]. The LOS, in turn, prevents gastric acid from refluxing into the oesophagus and causing damage to the oesophageal mucosa. Transient lower oesophageal sphincter relaxations (TLOSRs), triggered by gastric distension, are thought to be a major cause for gastro-oesophageal reflux disease (GORD). Gastro-oesophageal vagal afferents express gamma-aminobutyric acid (GABA) receptors of the $GABA_B$ type, activation of which reduces the mechanosensitivity of gastro-oesophageal vagal afferents involved in the reflex regulation of LOS tone [4]. The $GABA_B$ receptor agonist baclofen is very active in inhibiting TLOSRs and has been shown to ameliorate GORD in adults as well as children [5]. Stimulation of afferent neurons in the oesophagus by local administration of capsaicin improves motor performance of the oesophageal body in GORD patients with ineffective motility [6]. Thus, afferent neurons seem to contribute to the protection of the oesophageal mucosa from gastric contents in a dual manner: by regulating the competence of the LOS and by facilitating clearance of the oesophagus from refluxing acid (Figure 2).

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Spinal afferent nerve fibres as local emergency system in the gastrointestinal mucosa

There is ample evidence that afferent neurons originating from the dorsal root ganglia participate in the local regulation of GI circulation, secretion, motility, mucosal homeostasis and mucosal repair [1,7,8,9,10]. These tasks are accomplished by an efferent-like mode of operation: Calcitonin gene-related peptide (CGRP) is released from the peripheral fibres of sensory neurons and, in turn, modifies the activity of several GI effector systems. It has not yet been ascertained whether the efferent-like mode of action operates in parallel with the afferent mode of action of sensory neurons or whether different populations of sensory neurons subserve either an afferent or efferent-like function [11].

Although the local protective role of spinal afferent neurons has been demonstrated to take place in all regions of the GI tract from the oesophagus to the colon [7], most studies of this unique defensive action have been conducted in the gastroduodenal region. Here, the efferent-like mode of operation is best portrayed by the protective response of the gastric and duodenal mucosa to acid backdiffusion from the lumen into the mucosa [7,9]. If the mucosal barrier is disturbed or disrupted in the presence of luminal acid, the surge of acid intruding the lamina propria stimulates spinal afferents which via local CGRP release and nitric oxide (NO) formation cause prompt hyperaemia in the gastroduodenal mucosa, facilitate other mechanisms of defence such as bicarbonate (HCO_3^-) secretion and inhibit gastric acid secretion [1,7,8,9,12,13].

Further study of the efferent-like defensive action of sensory neurons has shown that the CGRP/NO messenger system stimulates mucin synthesis in the gastric corpus mucosa [14] and reduces myoelectrical activity in gastric smooth muscle [15]. Importantly, stimulation of sensory nerve fibres also exerts an anti-inflammatory action (Figure 3) which is brought about by a CGRP-induced increase in prostacyclin (PGI_2) formation and a decrease in tumour necrosis factor-alpha release and tissue accumulation of neutrophils [16]. Through this action, sensory nerve stimulation reduces stress-related gastric mucosal damage and ischaemia reperfusion-induced liver injury [16,17,18,19]. The protective role of sensory neurons is gender-dependent, given that oestrogen enhances the expression of CGRP in dorsal root ganglion cells and the availability of releasable peptide in the stomach, whereas ovariectomy reduces the expression of CGRP and makes the mucosa more vulnerable to stress-induced injury [17,19].

It is intriguing to note that some gastroprotective agents such as the histamine H_2 receptor antagonist lafutidine are able to stimulate sensory neurons, which may contribute to their gastroprotective effect [20,21]. The molecular mode of action whereby lafutidine excites sensory neurons, causes CGRP release and attenuates ethanol- and stress-induced gastric injury is different from that of capsaicin [20,21] but has not yet been elucidated. Sensory neuron dysfunction, to the contrary, impairs GI mucosal protection [7]. For example, the dwindling capacity of the gastric mucosa to defend itself against injury in ageing rats is associated with a reduced number of mucosal CGRP-containing nerve fibres and with a decreased ability of CGRP to facilitate gastric mucin synthesis [14]. Chronic gastritis appears to be associated with an enhanced expression of CGRP in the human stomach [22]

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and, in patients infected with *Helicobacter pylori*, symptoms of functional dyspepsia have been correlated with enhanced expression of CGRP and substance P in the antral mucosa [23]. The pathogenic relevance of these findings to the local inflammatory process awaits to be determined.

Molecular acid sensors of afferent neurons involved in the protection of the gastroduodenal mucosa

Most sensory neurons respond to extracellular acidosis. There is emerging evidence that the acid-sensitive ion channel TRPV1 (transient receptor potential vanilloid-1) plays a role in signalling for duodenal hyperaemia in the face of luminal acidification [24,25]. TRPV1 is expressed by many afferent neurons innervating the rodent and human GI tract [26,27,28,29,30,31,32]. Since TRPV1 is located on sensory nerve terminals in the lamina propria behind the epithelium, the mucosal acid signal must be transduced across the epithelium (Figure 3). This transepithelial signalling pathway involves CO_2 which is formed when excess luminal H^+ combines with HCO_3^- secreted into the mucosal gel layer [24,25]. Easily traversing the apical plasma membrane of epithelial cells, CO_2 is hydrated by carbonic anhydrase to carbonic acid which dissociates into HCO_3^- and H^+. H^+, in turn, exits via the basolateral sodium-proton exchanger-1 and lowers interstitial pH, which activates TRPV1-bearing sensory nerve fibres that release the vasodilator peptide CGRP [24,25].

The implication of TRPV1 in neural acid sensing has previously been envisaged from the effect of capsaicin, a ligand known to stimulate TRPV1 [26]. Thus, the *capsaicin*-evoked gastric hyperaemia [33] gastric mucosal protection [34,35] and gastroduodenal bicarbonate secretion [12,36] are antagonized by the TRPV1 blocker capsazepine. Unlike the *acid*-induced hyperaemia in the duodenum [24], the *acid*-evoked secretion of bicarbonate [12] and hyperaemia in the rat stomach [33] remain unaltered by capsazepine. This finding does not totally rule out any implication of TRPV1 because capsazepine is a class B blocker of TRPV1, inhibiting channel activation by capsaicin more potently than that by acid. It is, however, conceivable that there are regional differences in the receptor mechanisms whereby acid challenge activates sensory neurons, a conjecture that is in keeping with the multiplicity of acid-sensing ion channels expressed by sensory neurons [37].

Acid-sensing ion channels (ASICs) comprising ASIC1, ASIC2 and ASIC3 represent another class of molecular acid sensors present on primary afferent neurons in the GI tract [27,38]. While ASIC3 participates in the inflammation-induced hypersensitivity of vagal afferents to gastric acid [39] and spinal afferents to colorectal distension [40], it has not yet been examined whether sensory neuron-mediated GI mucosal protection involves ASIC3.

Mucosal factors stimulating afferent neurons involved in gastric mucosal protection

Bradykinin, ghrelin and melatonin have been identified as factors that facilitate GI mucosal protection through sensory neuron-dependent mechanisms. The effect of bradykinin to stimulate gastroduodenal HCO_3^- secretion through an action involving sensory neurons is mediated by bradykinin B_2 receptors and prostaglandin E_2 [12,13]. Ghrelin is produced by

endocrine cells of the gastric mucosa and known to excite vagal afferents which express ghrelin receptors [41]. The ability of this peptide to attenuate ischaemia reperfusion-induced injury in the gastric mucosa involves activation of sensory neurons and formation of NO [42]. Melatonin, which likewise is a GI hormone, attenuates stress-induced gastric lesions through stimulation of melatonin MT_2 receptors and CGRP-releasing sensory neurons [43].

Pro-inflammatory effects mediated by sensory neurons in the gut

Despite the evidence that primary afferent neurons releasing CGRP contribute to GI mucosal defence, this functional implication must not be generalized because there is evidence that under certain conditions sensory neurons exacerbate inflammatory tissue reactions. For instance, gastritis induced by iodoacetamide or diquat is significantly reduced by capsaicin-induced ablation of sensory neurons [44] and colitis evoked by dextrane sulfate sodium is attenuated by TRPV1 blockers [45]. Likewise, ileitis induced by *Clostridium difficile* toxin A or the endocannabinoids anandamide and 2-arachidonoyl glycerol is ameliorated by capsazepine [46], and pancreatic islet inflammation in an experimental model of type-1 diabetes is inhibited by ablation of TRPV1-expressing sensory neurons [47]. In contrast, the effect of dinitrobenzene sulfonic acid to induce colitis and disturb colonic smooth muscle activity is increased in TRPV1 knockout mice [48].

The proinflammatory role of TRPV1-bearing sensory neurons in the ileitis evoked by *Clostridium difficile* toxin A is thought to arise from the formation of endocannabinoids which stimulate TRPV1 and thereby cause the release of substance P from sensory nerve fibres [46]. Substance P, in turn, activates enteric neurons and immune cells, which ultimately results in hypersecretion, inflammation and mucosal damage [46]. Whether hydrogen sulfide contributes to these processes awaits to be determined. Formed by cystathionine gamma-lyase and cystathionine beta-synthase in enteric neurons, hydrogen sulfide enhances intestinal chloride secretion via an action involving TRPV1 and capsaicin-sensitive afferent neurons [49].

The vagal anti-inflammatory reflex

Cytokine-responsive vagal afferent neurons participate in the communication between the peripheral immune system and the brain [50,51]. This function is supported by a particular proximity of vagal afferent nerve fibres to immunologically relevant structures such as hepatic Kupffer cells (macrophage-like cells), paraganglia and connective tissue containing macrophages and dendritic cells [50,51]. Bacterial lipopolysaccharide (endotoxin) is able to cause release of interleukin-1beta from these cells, the cytokine in turn leading to excitation of vagal afferents [50,51].

Through these properties, vagal afferents are thought to mediate a vago-vagal anti-inflammatory reflex (Figure 4). Peripheral immune and inflammatory signals trigger an input to the brain both via vagal afferents and circumventricular organs that are devoid of a blood-brain barrier. These signals are processed by the brainstem and central autonomic circuitries to provide an output via cholinergic vagal efferents [52]. Acetylcholine, released from efferent axons in the periphery, activates alpha7 subunit-containing nicotinic receptors on tissue macrophages and other immune cells (Figure 4), which results in inhibition of pro-

inflammatory cytokine release and suppression of inflammation [52,53]. The specific involvement of alpha7 subunit-containing nicotinic receptors makes it conceivable that alpha7 subunit-selective agonists such as GTS-21 represent a new type of anti-inflammatory agent that is devoid of an action on autonomic ganglia in which transmission is mediated primarily by alpha3/beta4 subunit-containing nicotinic receptors [54].

There is emerging evidence that the vagovagal anti-inflammatory reflex has an important role in controlling inflammation within the gut. Thus, dextrane sulfate sodium-induced colitis is exaggerated by vagotomy and hexamethonium and attenuated by nicotine [55]. The anti-inflammatory action of the vagus nerve involves a macrophage-dependent mechanism, because vagotomy fails to exacerbate colitis in mice that are deficient of macrophage colony-stimulating factor [55]. The extent of inflammation following abdominal surgery is a factor relevant to the severity and duration of postoperative ileus. Stimulation of nicotinic acetylcholine receptors has been reported to inhibit macrophage activation, ameliorate surgery-induced inflammation and reduce postoperative ileus through downstream activation of the Jak2-STAT3 signalling pathway [56].

Conclusions

The role of primary afferent neurons in monitoring actual or potential threats to the GI mucosa is of physiological relevance to body homeostasis. Long thought to subserve primarily nociception, sensory neurons are now recognized to enforce GI mucosal defence through several mechanisms (Figure 1), among which autonomic reflexes and the initiation of protective tissue reactions at the site of insult play a particular role. Significant progress has been made in the past years to identify the molecular sensors that enable afferent neurons to recognize potential threats. These nocisensors include TRPV1 and ASIC3 and receptors for local tissue mediators (e.g., bradykinin, ghrelin, melatonin, endocannabinoids, hydrogen sulfide) that are released upon challenge of the GI tract.

Autonomic reflexes that govern motor and immune functions of the GI tract are fine-tuned by the multiple sensory capacities of their afferent arm. For instance, the passage of gastric juice across the LOS and pyloric sphincter is controlled by chemo- and mechanosensitive afferent neurons that may be targeted in the design of novel GORD therapeutics. A particular aspect of GI homeostasis is highlighted by the discovery of vago-vagal anti-inflammatory reflexes that have a bearing on GI immune function. Since the anti-inflammatory reflex output to GI immune cells is mediated by alpha7 subunit-containing nicotinic receptors, it appears possible to develop alpha7 subunit-selective agonists as a new type of anti-inflammatory agent.

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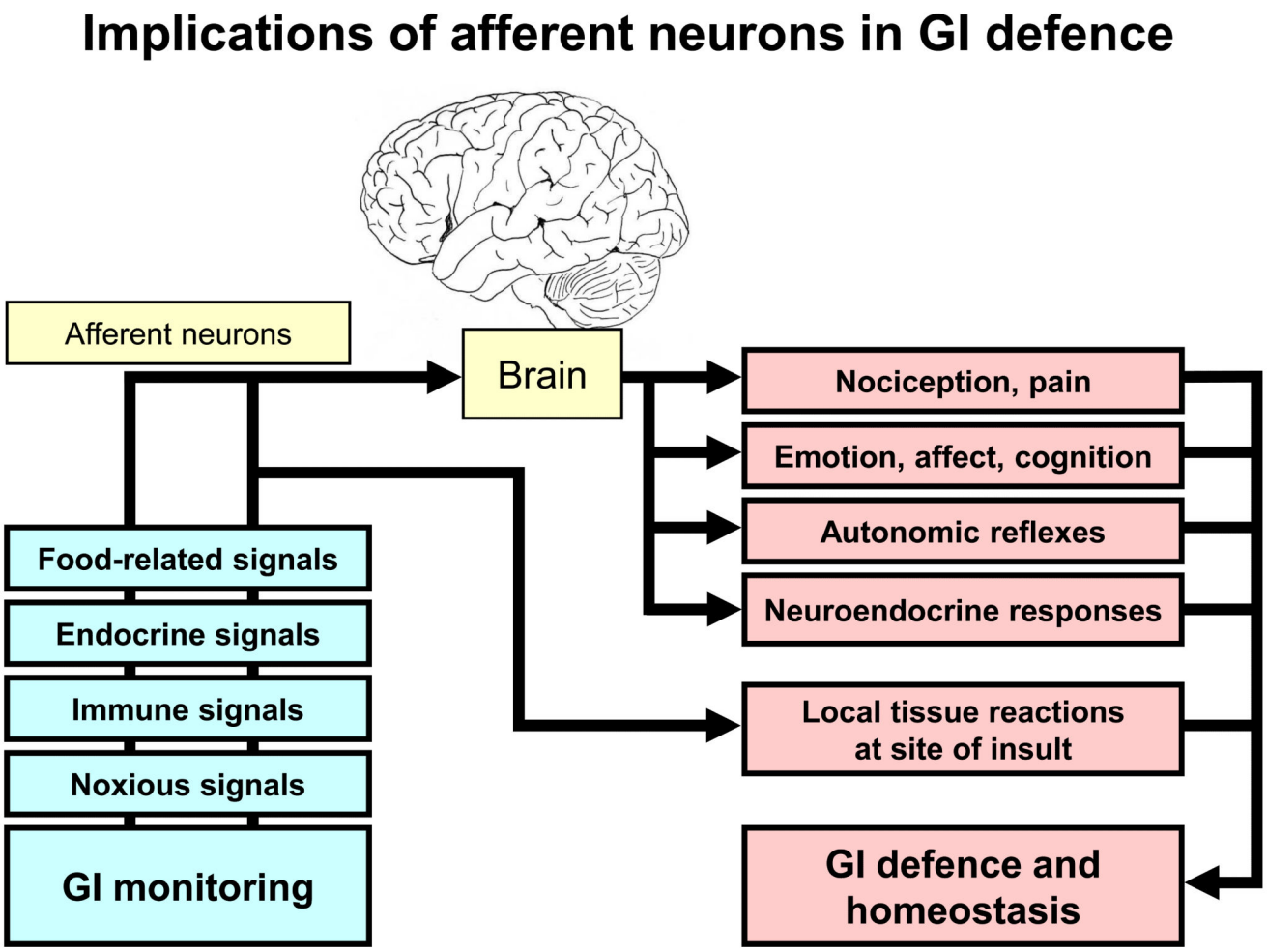

Figure 1.

Implications of afferent neurons in gastrointestinal (GI) defence. The graph shows that primary afferent neurons monitor the chemical and physical environment within the GI tract as they are able to respond to a variety of signal modalities. Via brain-mediated reactions and reflexes and through local neuropeptide release at the site of insult they contribute to GI defence and homeostasis.

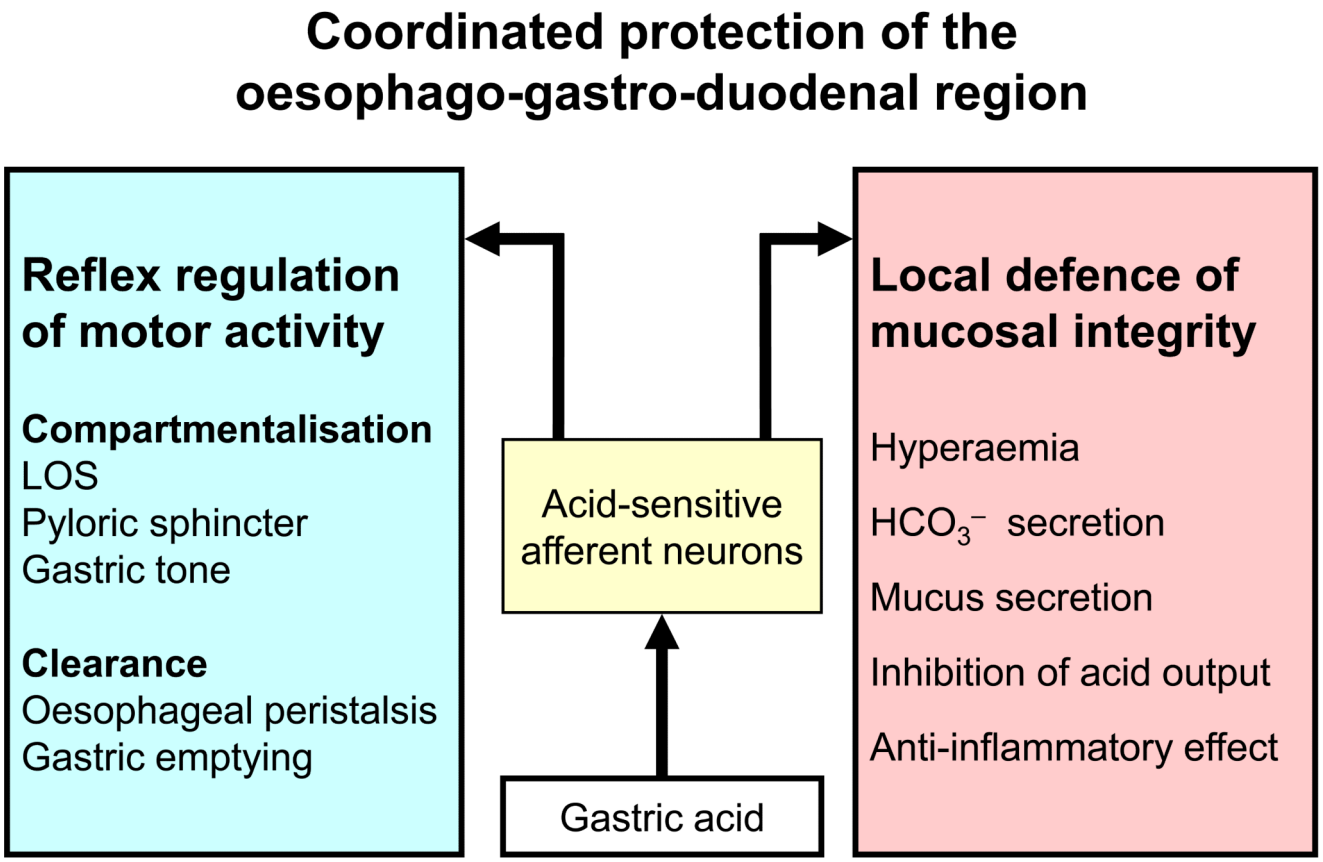

Figure 2.
Coordinated protection of the oesophago-gastro-duodenal region. The graph shows that acid-sensitive afferent neurons protect the foregut from gastric acid by reflex regulation of motor activity in the lower oesophageal sphincter (LOS), stomach and pyloric sphincter and by governing local tissue reactions supporting the defence of the mucosa.

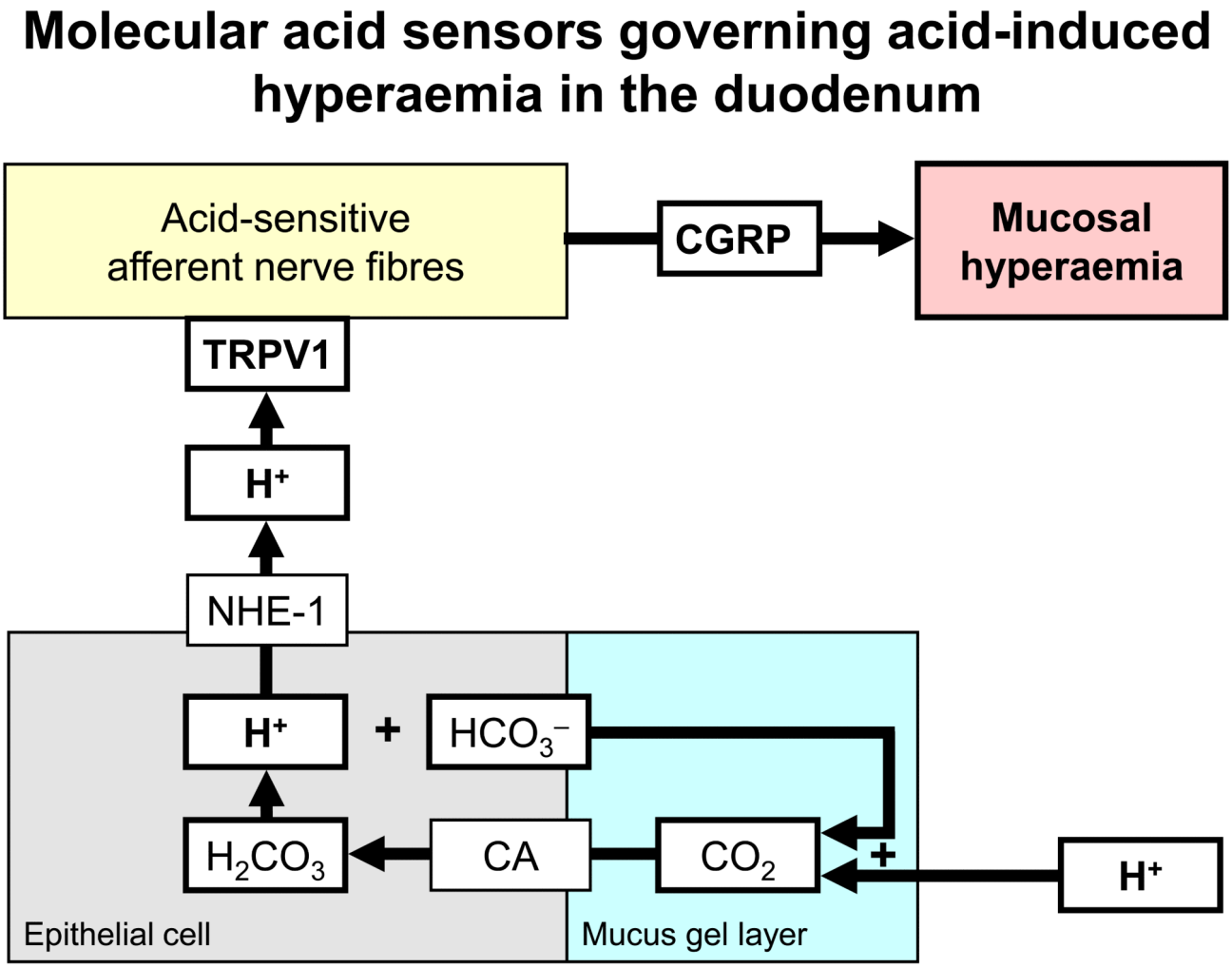

Figure 3.

Molecular acid sensors governing acid-induced hyperaemia in the duodenum [24]. The graph shows that luminal acid diffusing into the mucus gel layer of the duodenal mucosa interacts with HCO_3^- to form CO_2. This molecule easily traverses the apical plasma membrane of epithelial cells where it is hydrated to carbonic acid by carbonic anhydrase (CA). Carbonic acid dissociates into HCO_3^- and H^+ which exits the cells via the basolateral sodium-proton exchanger-1 (NHE-1) and lowers interstitial pH. Subepithelial acidosis activates TRPV1-bearing sensory nerve fibres that release the vasodilator peptide CGRP.

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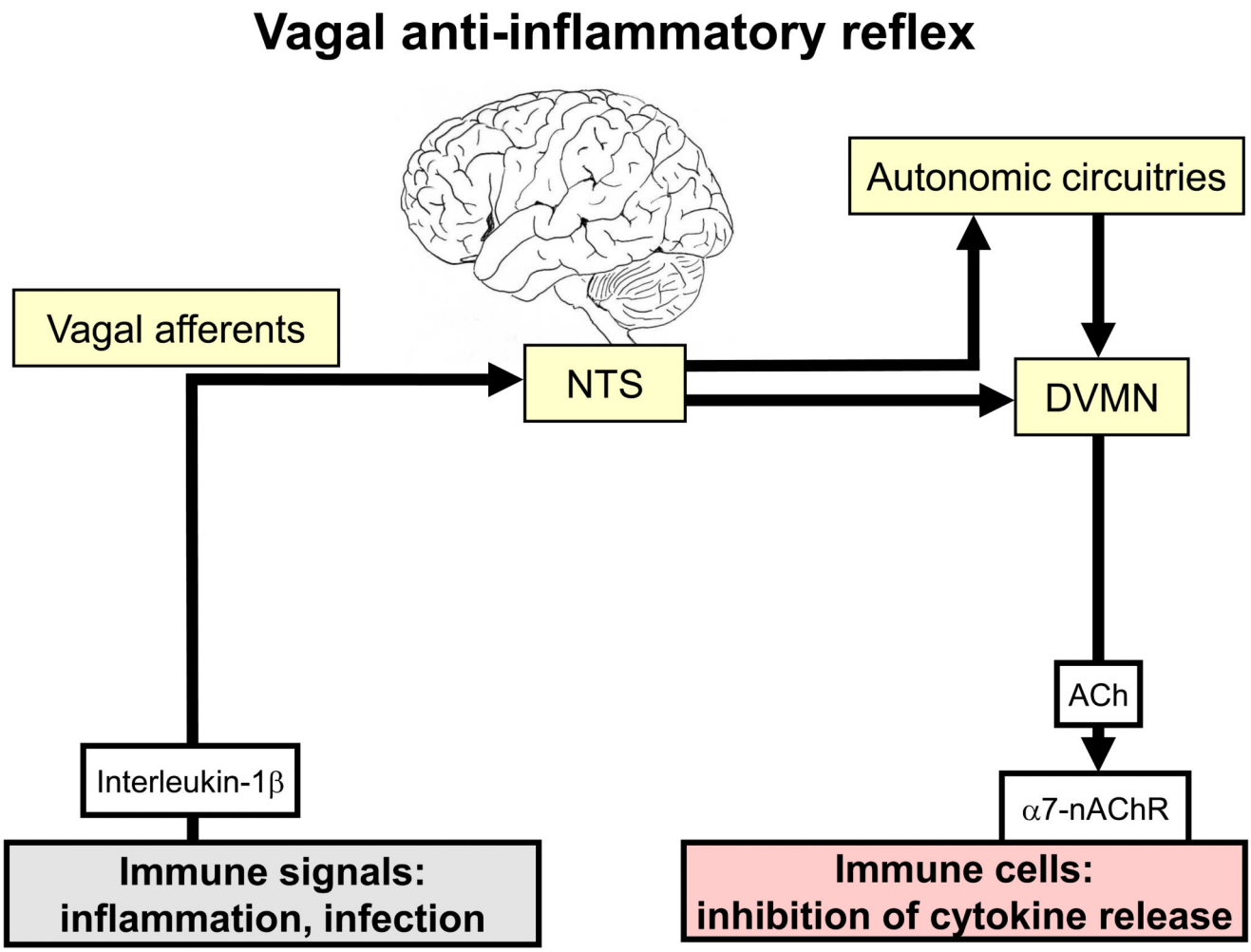

Figure 4.

Vagal anti-inflammatory reflex [52]. The graph shows a vago-vagal reflex, the afferent arm of which is activated by pro-inflammatory cytokines such as interleukin-1beta. Following processing in the nucleus tractus solitarii (NTS) and in autonomic circuitries of the brain, efferent output is generated from the dorsal vagal motor nucleus (DVMN). Acetylcholine (ACh) released from vagal efferents activates alpha7 subunit-containing nicotinic acetylcholine receptors (alpha7-nAChR) on macrophages and other immune cells, which results in inhibition of pro-inflammatory cytokine release.