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Plasticity of vagal afferent signaling in the gut

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Abstract

Vagal sensory neurons mediate the vago-vagal reflex which, in turn, regulates a wide array of gastrointestinal functions including esophageal motility, gastric accommodation and pancreatic enzyme secretion. These neurons also transmit sensory information from the gut to the central nervous system, which then mediates the sensations of nausea, fullness and satiety. Recent research indicates that vagal afferent neurons process non-uniform properties and a significant degree of plasticity. These properties are important to ensure that vagally regulated gastrointestinal functions respond rapidly and appropriately to various intrinsic and extrinsic factors. Similar plastic changes in the vagus also occur in pathophysiological conditions, such as obesity and diabetes, resulting in abnormal gastrointestinal functions. A clear understanding of the mechanisms which mediate these events may provide novel therapeutic targets for the treatment of gastrointestinal disorders due to vago-vagal pathway malfunctions.

Keywords

Digestive system; Gastrointestinal peptides; Sensory innervation; Nodose ganglia neurons

1. Introduction

Vagal afferents play an important role in the regulation of the physiological functions of the gastrointestinal (GI) tract. Studies have revealed that stimulation of gastric vagal afferents initiates a number of vagally mediated reflexes, including suppression of food intake [1], inhibition of gastric emptying [2], stimulation of acid [3], and pancreatic secretion [4]. The vagus afferents may be stimulated by gastric distension, an array of gut hormones released from the enteroendocrine cells (ECs) in response to food intake, or may be directly activated by nutrients such glucose, fatty acids or salts in the gut [5–9]. Vagal sensory signaling includes events such as the encoding, integration, and transfer of peripheral sensations by vagal afferent neurons to the CNS.

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Conflicts of interest

The authors declare no conflicts of interest.

Over the last decade it has become clear that vagal afferent neurons exhibit remarkable plasticity in response to intrinsic and extrinsic factors. For example, recent works by the Docray's group showed that nutritional status regulates receptor density and neuromediators expressed by the vagal neurons. This in turn determines the neuro chemical phenotype of the vagal afferent neurons. Depending on the nutritional status, the same group of afferent neurons may transmit orexigenic or anorexigenic signals [10–12]. Furthermore, it is well known that vagal afferent neurons exhibit abnormal sensitivity to GI peptides or mechanical stimuli in pathological conditions such as diet-induced obesity or diabetes [13–17].

The aim of this article is to review some of the newer concepts regarding the role of vagal afferents in the regulation of gut functions. Plasticity of vagal afferent signaling provides an added level of fine tuning in response to the nutritional and metabolic status of the subject. These pathways also suggest new approaches and targets for the treatments of obesity and GI tract disorders.

2. Vagal sensory innervation of the gut

Cell bodies of vagal afferent neurons reside in two adjacent but distinct anatomic structures: the nodose (inferior) and intracranial jugular (superior) ganglia. Vagal neurons from the nodose ganglia originate from the epibranchial placodes, while jugular neurons originate from the neural crest [18]. Visceral afferents can be classified by the location of their receptive fields (mucosal afferents, muscle afferents), their function (low and high threshold mechanoreceptors, termo-, osmo-sensitive, chemoreceptors, nociceptors), their conduction velocities (C-, Aδ- and Aβ fibers), or their neurochemical codings (peptidergic and non-peptidergic afferents) [19–22]. In addition, many visceral afferents respond to a wide range of mechanical and chemical stimuli, and are considered "polymodal" [23–27]. Vagal sensory fibers do not appear to mediate pain sensation in the gut, since it has been shown that severing the spinal, but not the vagal, pathway abolished pain sensations induced by colon or stomach extension or heat [20,28,29]. However, more recent data suggests that vagal afferents may mediate mechanical or acid-evoked esophageal nociception [30–33].

Electron microscopic and physiologic studies demonstrate that visceral sensory fibers are predominantly unmyelinated (C-fibers) and few are thinly myelinated axons (Aδ fibers) [21,33,34]. Antegrade tracing studies showed that vagal afferent nerve endings are widely distributed in the mucosal layers of the stomach and proximal small intestine. These endings are observed in the villi, with some fibers approaching the basal side of epithelial cells [35,36]. It is likely that these vagal mucosal afferents express polymodal sensitivity to light mechanical stimuli, but not to stretching [24,25,37–39]. They can sense osmotic and thermal changes [23,40–43] and have chemosensitive properties to amino acid and glucose [43,44]. About a third of these afferents respond to capsaicin, a vanilloid receptor agonist, which is prevalent in c- and Aδ fibers [19,26,38,39,45]. It should be noted that most nutrients activate EC, triggering the release of mediators such as CCK, serotonin (5HT), and leptin which, in turn, activate/modulate mucosal afferent fiber terminals.

Morphological tracing studies reveal a second type of afferent endings within the muscular layers of the gut. These endings have been shown to be closely associated with the

intramuscular interstitial cells of Cajal (ICC), which leads to the speculation that they may act in conjunction with the ICC to form a functional complex [46] to detect tension and monitor gut distension [47].

The responses to vagal afferent stimulation depend on the sites of stimulation. For example, stimulation of esophageal vagal afferents causes fundus relaxation [48,49], while stimulation of vagal fibers in the stomach or ileum results in inhibition of food intake, gastric emptying, and stimulation of pancreatic secretion [50]. Grabauskas et al. [7] recently demonstrated that increase in the extracellular glucose concentration excited 30% of the stomach projecting nodose ganglia neurons but inhibited 11% of the portal vein projecting neurons.

In general, hormonal and chemical stimuli from the stomach modulate gastric vagal afferent responses to mechanical stimulation, whereas the small intestine hormones directly activate vagal afferent endings. Both the modulatory and direct actions of these hormones on gut afferents may activate or inhibit satiety. Moreover, it is suggested that mechanoreceptors within the stomach are the only means by which the stomach sends afferent signals to the brain [26,51,52]. The consumption of food would cause distension of the stomach and is perceived centrally with well-characterized feelings of fullness and satiety [53] which can be modulated by gut peptides; for example, CCK augments and ghrelin dampens mechano-responses of sensory fibers [9]. In a recent study Kentish et al. [17] demonstrated the expression of clock genes (*Bmal*1, *Per*1, *Per*2, and *Nr*1*d*1) in vagal afferent cell bodies, and that oscillation of the expression of these genes correlates with changes in gastric mucosal receptor sensitivity to stroking. Single fiber recording from stomach projecting afferents demonstrated that gastric mucosal receptor response to stroking with a Frey's hair is 3 times greater at 12 h and 15 h than the response at 0 h. Thus, gastric vagal mechanoreceptors display circadian rhythm, which may act to control food intake differentially at different times of the day.

3. Regulation of vagal sensory neurons by gut peptides

Gut peptides are major regulators of vagal sensory activities. These include cholecystokinin (CCK), ghrelin, and leptin that are expressed and released from discrete populations of GI enterochromaffin cells (Table 1). These peptide secreting cells are located close to vagal afferent sensory endings [9] which express a number of gut hormone receptors (Fig.).

3.1. CCK

CCK is released from enterochromaffin (EC) I-cells, located largely in the proximal small intestine in response to luminal nutrients such as amino acids and fatty acids [90–92]. CCK evokes contraction of the gallbladder [54,55], and stimulates pancreatic enzyme secretion [56,57], and inhibition of food intake [58,59].

Expression of both high affinity CCK receptor (CCK1) and low affinity CCK receptor (CCK2), has been demonstrated in the vagal afferent fibers and vagal neuronal soma [93–98] (Fig.). Within the mucosa, vagal afferents expressing the CCK1 receptor terminate within the lamina propria in close apposition to the basolateral membrane of I cells [99,100]. Electrophysiological studies demonstrate that the vagal afferent discharge is increased by

CCK-8 [4,40,79,86,101] and similarly, neurons in the nucleus tractus solitarii (NTS) that receive inputs from vagal afferents are stimulated by CCK [102–105].

There is ample evidence that the majority of CCK actions are mediated by activation of CCK 1 and 2 receptors in the vagal afferents [4,60,106–108] (Fig.). It has been demonstrated that pretreatment of vagus with the neurotoxin capsaicin, or total subdiaphragmatic vagotomy, attenuated the reduction in cumulative food intake evoked by CCK-8 and −33 [5,109–112]. Disruption of the vagal afferent pathways markedly reduced the CCK satiety action in both rats and mice. The CCK1 receptor knockout Otsuka Long-Evans Tokushima Fatty (OLETF) rats are hyperphagic [113]. Similar to OLETF rats, CCK1 receptor knockout mice consume larger meals [114]. However, in this model the role of CCK1 receptors to maintain normal body weight is less critical, despite evidence that CCK plays a major role in satiety

Li and Owyang [4] demonstrated that perivagal pretreatment with capsaicin or transection of afferent nerves abolished the pancreatic enzyme response to physiological doses of CCK-8. This provides strong evidence for neuronal action of endogenous CCK, acting via an afferent vagal pathway in the duodenal mucosa to stimulate pancreatic secretion in the rat [87,115]. However, this approach was recently challenged by the demonstration that perivagal application of capsaicin may cause degeneration of vagal efferent motoneurones [116]. It is interesting to note that the dorsal motor nucleus of the vagus (DMV) may also be activated by CCK-8 [117] raising the possibility that pancreatic secretions are under the modulatory control of CCK responsive vagal motoneurones [117]. In any case, there is strong evidence that CCK is acting via vagal pathway to stimulate pancreatic enzyme secretion [115].

3.2. Leptin

Leptin is a 127-amino acid peptide mainly secreted by adipocytes [118] and to a lesser degree from the gastric parietal (P) cells [119]. Leptin is known to suppress appetite, body weight gain, and adiposity in humans, rodents, and monkeys [120]. Leptin receptors (LRbs) are found in a variety of brain areas and predominantly in areas with documented roles in feeding control [121,122] (Fig.). LRbs are also expressed by vagal afferents terminating in the stomach. Indeed, leptin has been shown to directly activate cultured gastric and duodenum projecting vagal afferents from rats [79,123–125]. This suggests that leptin released from the gastric mucosa could act on adjacent vagal afferent endings to modulate vagal signals in response to food intake. Experiments have demonstrated that leptin reduced short-term (up to 4 h) food intake which required intact vagal nerves [61,62,126]. Targeted deletion of leptin receptor in vagal sensory ganglia in mice led to a small but significant increase in body weight at 10 weeks and with further weight gain at 12 weeks as a result of increased fat mass [13,127]. These observations indicate that vagal action of gastric leptin may serve to augment the acute appetite-suppressant effects of circulating leptin [123,128].

3.3. Ghrelin

Ghrelin is a 28-amino acid peptide secreted from the X/A cells found predominantly in the stomach and to a lesser extent in the intestine [129–131]. Feeding studies indicate that

ghrelin participates in the regulation of food intake, body weight, adiposity, insulin secretion, glucose metabolism and GI functions such as stimulation of gut motility and gastric acid secretion [63–68] (Table 1).

Ghrelin actions are mediated by the growth hormone secretagogue receptor (GHS-R), a G-protein-coupled receptor (GPSR) [129,132]. Two isoforms of GHSR – 1a and 1b – have been identified but only GHSR1a is considered as the active form of GHSR. GHSR1a is densely expressed in the hypothalamus, the substantia nigra, the ventral tegmental area and throughout the limbic system [129,133] and cell bodies of the enteric nervous system [134]. The GHSR1a receptor also found in the mouse nodose ganglia and in vagal afferents that project to the stomach [69,70,79] (Fig.). Anterograde tracing studies demonstrated that vagal afferents are found in close proximity to ghrelin-containing cells in the mice stomach mucosa [16]. Moreover, it was reported that ghrelin selectively inhibited a subpopulation of mechanosensitive gastric vagal afferents [135], supporting the possibility that there is a close functioning relationship between ghrelin and gastric vagal afferent generated satiety signals.

The vagus is important in mediating the actions of ghrelin on gastric functions (Table 1). Treatment with atropine, capsaicin or vagotomy abolished the effects of peripherally administered ghrelin on food intake, gastric emptying, intestinal transit, and gastric acid secretion [63,64,69,71,72]. Recently, Grabauskas et al. [79] demonstrated that targeted deletion of the Kir6.2 subunit, which is an integral part of the ATP-sensitive potassium channel (K_{ATP}), in the vagal nodose ganglia abolished the orexigenic action of ghrelin on food intake. Also, it was demonstrated that ghrelin action to reduce vagal afferent activities of neurons is mediated by the GHSR-1a receptor-phosphatidylinositol 3-kinase (PI3K)-extracellular signal-regulated kinase 1 and 2 (ERK1/2)-K_{ATP} channel signaling pathway. The resulting hyperpolarization renders the nodose ganglia less responsive to anorexigenic signals that act via the vagal afferent pathways [70,136].

Recently, the role of the vagus in mediating the actions of ghrelin was brought into question by the observation that subdiaphragmatic vagal deafferentation did not abolish the hyperphagic action of ghrelin [137]. However, it is important to point out that this observation does not rule out the possibility that ghrelin may act directly on the vagal sensory neuron soma to modulate satiety [79]. The identification of the specific signaling pathways used by ghrelin on the vagus sensory neurons provides an opportunity to develop agents to modulating food intake via peripheral pathways. This potentially may be used to treat feeding disorders.

4. Receptor interaction

4.1. Feeding status modulates neurochemical phenotype of vagal sensory neurons

Feeding status may have a profound influence on the actions of gut peptide regulating GI functions by changing the expression of receptors and/or neurotransmitters. For example, under fasting conditions when basal plasma CCK level is low, there is increased expression of vagal cannabinoid CB1 and melanin-concentrating hormone (MCH)-1 receptors and low expression of Y2 receptors which respond to the satiety peptide YY (PYY) [10–12,138]. Fasting also causes an increased expression of the orexigenic neuropeptide MCH and

decreased expression of the satiety-induced peptide cocaine and amphetamine regulated transcript (CART). On the other hand, feeding rapidly downregulates the expression of CB1 and MCH-1 receptors but enhances the expression of Y2 receptors in vagal neurons projecting to the stomach and duodenum. This is accompanied by decreased expression of MCH and increased expression of CART but stable expression of CCK1, orexin receptor type 1 (Ox1) and GHR1 receptors [10,50,70,136,139]. These phenotypic changes appear to be mediated by CCK as they can be blocked by CCK1 receptor antagonists and reproduced by exogenous CCK administration [10–12,14,50]. These findings indicate that neuro chemical phenotype of vagal afferent neurons can be altered depending on the feeding status.

4.2. Synergistic interactions between gut neuromediators in vagal ganglia

It is well established that a variety of gut-derived mediators interact to enhance each other's activity on vagal afferent neurons. Rodent studies showed that leptin injected intraperitoneally at low doses, which did not influence feeding behavior, decreased foodintake and body weight when co-injected with a subthreshold dose of CCK [61,125,140–144]. In fact, it was suggested that the satiety action of CCK appears to depend on leptin signaling. This synergistic leptin-CCK interaction was reported to be associated with an increase in the firing frequency of gastric vagal sensory neurons [108,144–146] and accompanied by increased activation of early gene c-fos expression in the NTS of the brainstem [61,140,144,147,148], the paraventricular nucleus and the dorsomedial nucleus of the hypothalamus [149]. The anorexigenic action of leptin and CCK was attenuated by capsaicin treatments and pretreatment with the specific CCK1 receptor antagonist [61], suggesting that CCK and leptin interact at the vagal fibers.

Heldsinger and colleagues [146] recently demonstrated that the synergistic interaction between vagal CCK and leptin receptors is mediated by the phosphorylation of signal transducers and activation of transcription 3 (STAT3), which in turn, inhibits potassium channels, leading to neuronal firing in isolated rat vagal neurons. This involves the interaction between CCK/SRC/phosphoinositide 3-kinase cascades and leptin/janus kinase-2/phosphoinositide 3-kinase/STAT3 signaling pathways. This synergistic interaction stimulates CART release from the vagal sensory neurons, which is the principal neurotransmitter mediating short-term satiety [150,151].

Leptin appears to act on both peripheral and central sites to exert its control on satiety. It was demonstrated that peripheral administration of leptin reduced acute sucrose intake whereas central administration had no effect [125]. Other studies showed that the acute effect of leptin on food intake is due to its ability to activate vagal afferents [152]. Selective knockout of the leptin receptor in visceral afferents caused hyperphagia leading to increased weight gain further affirming that leptin is acting on sensory vagal fibers to regulate food intake [127].

Leptin also has been shown to act on the hypothalamic nuclei to potentiate the peripheral action of CCK [153]. Morton and colleagues showed that leptin receptor-deficient Koletsky rat, in which the LRb in the medial basal hypothalamus, a site that has been implicated in the feeding action of leptin was specifically deleted, had a reduced satiety response to peripheral

CCK. The targeted restoration of leptin signaling in the basal medial hypothalamus both reduced the size of meals and made the Koletsky rat more responsive to exogenous CCK. These observations indicate that CCK and leptin may also interact at the hindbrain/brainstem integrative sites raising the possibility that leptin and CCK may generate anorexic signaling at multiple sites.

In addition to leptin, CCK also interacts with other gut hormones to regulate GI function. Using the single vagal afferent neuronal recording, Li and colleagues [86] demonstrated that in about 50% of recorded vagal neurons although a subthreshold dose of CCK-8 produced no measurable electrophysiological effects, it augmented vagal firing in response to luminal 5-HT perfusion. This interaction between CCK and 5-HT at the level of the vagal ganglia may modulate afferent postprandial signals arising from the GI tract and may explain how a small increase in the plasma CCK level is sufficient to produce a robust postprandial pancreatic secretion [60]. This interaction would also explain how CCK administration potentiates subsequent responses to GI perfusion of nutrients [2,43,101,108].

The anorexigenic hormones leptin and CCK, and the orexigenic hormone ghrelin act in opposition to regulate feeding behavior via the vagal afferent pathways. Feeding studies demonstrated that the anorexic effect of CCK was blocked by pre-administration of ghrelin in rats. Conversely, pretreatment with CCK inhibited the orexigenic effect of ghrelin [12,50,70,137]. Since CCK1 and GHSR1a are colocalized in the nodose ganglia neurons, it is conceivable that CCK and ghrelin may interfere with signal transmission generated by one another at the level of vagal nodose neurons. Studies of the signaling cascades used by ghrelin showed that ghrelin caused a significant increase in Epac and suppression of cytokine signaling 3 (SOCS3) expression in cultured rat nodose ganglia [146]. This in turn negatively affects leptin signal transduction and neuronal firing in vagal neurons. Feeding studies showed that silencing SOCS3 expression in the vagal ganglia reduced food intake evoked by endogenous leptin.

5. Central projections of visceral afferents

Visceral sensory information is transmitted via the vagal afferent fibers to the nucleus of the tractus solitaries (NTS) in the hindbrain [49,154]. Gut innervating vagal afferents which terminate in the NTS are organized topographically: terminates from the esophagus project predominantly to the subnucleus centralis, those from the stomach project to the subnucleus medialis and gelatinosus and terminals from the intestine are represented in the subnucleus commissuralis and medialis [155–157].

Glutamate is the main neurotransmitter utilized by the vagal afferents to communicate with the second order neurons in the NTS [158] (Table 2). Approximately 60% of the vagal sensory neurons somas [172,173] and terminals in the NTS [174] contain glutamate immunoreactivity. NTS neurons express both sonotropic (N-methyl-D-aspartate [NMDA], α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor [AMPA], kainite) and metabotropic glutamate receptors [175–177]. Blocking of NMDA receptors with systemic or intra-NTS microinjection of NMDA antagonist, dizocilpine delayed satiation and increased

meal size [178–180]. Additionally, CCK-induced satiation was also attenuated by NTS injection of the NMDA receptor antagonist MK801 [181,182].

CART is another neuropeptide implicated in central vagal transmission (Table 2). Immunohistochemical studies demonstrated that 17% of the vagal sensory neurons with gastric projections and 41% of those projecting to the duodenum expressed CART immunoreactivity [182]. These CART containing vagal neurons also coexpressed CCK1 and LRb. Functionally, CCK and leptin stimulated CART release from vagal terminals to mediate satiety [150]. It was shown that injections of CART into the 4th ventricle greatly suppressed food intake and the drinking of sucrose water accompanied by inhibition of C-Fos expression in the NTS [182]. Conversely, targeted silencing of CART with siRNA in the rat nodose ganglia abolished CCK and leptin stimulated C-Fos expression in the hypothalamus and CCK/leptin induced satiation [150]. Thus, in addition to glutamate, CART is another neuropeptide utilized by the vagal afferents to transmit peripheral signals to activate NTS in the brain stem.

Synaptic transmission between the vagal afferents and NTS neurons is subject to modulation by a wide variety of neurotransmitters, hormones and metabolites including glutamate [183–186], CCK [187,188], tumor necrosis factor [189], melanocortins [190], 5HT [191], ATP [192], and prostaglandins [193]. Second order sensory neurons in the NTS project either locally to the DMV, which innervate the gut, or send ascending projections to the forebrain including the parabrachial nucleus, hypothalamus, amygdala, nucleus of the stria terminalis and insular cortex [194]. In addition to vagal afferents, the NTS neurons also interact with each other and with neurons in other CNS areas and hormones to fine tune synaptic transmission between NTS and DMV [159,195–200]. In this way, the NTS neurons can respond to constantly changing physiological conditions to regulate gut function.

6. Vagal afferent pathways in clinical conditions

6.1. Diabetes modulates excitability of vagus

GI functions are often abnormal in patients with poorly controlled diabetes. These include impaired esophageal motility, defective gastric accommodation, abnormal gastric emptying, diminished pancreatic function, and abnormal eating behavior. Many of these functions are mediated by vago-vagal pathways. Abnormalities of vagal function are common in patients with longstanding diabetes, although anatomical abnormalities are seldom demonstrable on histologic examination of the vagus. This raises the possibility that vagal dysfunction may be secondary to altered electrophysiological properties of the nodose ganglia (NG) caused by chronic hyperglycemia. Two-pore-domain potassium ($2PK^+$) channels play an important role in setting the resting membrane potential and excitability of neurons. Regulation of $2PK^+$ channels by neurotransmitters and second messengers is essential for neuronal functioning in the central nervous system [201].

In a recent study, it was demonstrated that the TRAK-related spinal cord K^+ channel (TRESK) is abundant in rat NG and its activation is increased in diabetic rats [201]. Enhanced activation of the TRESK K^+ channel in the capsaicin-sensitive NG of diabetic rats led to membrane hyperpolarization, resulting in decreased excitability and abnormal GI

functions mediated by the vago-vagal reflex such as pancreatic enzyme secretion and gastric motility. Silencing the TRESK K^+ channel in the diabetic rat restored NG excitability and improved GI functions mediate by vago-vagal reflex. These findings provide an attractive unifying hypothesis to explain the widespread GI disturbances in diabetic patients. Understanding the signal transduction cascade mediating the abnormalities may provide important therapeutic targets for the medical treatment of diabetic patients with GI complications.

6.2. High fat feeding induces dysfunction of the vagus

Altered function of the vagal afferent pathways occurs in obesity. Gastric [16] and jejunal [15] vagal afferents showed reduced responsiveness to mechanical stimulation in high fat diet-induced obese mice. This was accompanied by diminished satiety action of CCK [15,202,203] and reduced c-fos expression in the area postrema and nucleus of the solitary tract [203].

Reduced anorexigenic response also applies to leptin stimulation [196,197] in diet-induced obesity where there was a 94% reduction of receptor expression [32]. The potentiating effect of leptin on the mechanosensitivity of mucosal receptors was abolished in high fat induce obese mice [16,160,204]. On the other hand, the inhibitory action of ghrelin was enhanced as the mucosal and tension afferents became more sensitive to ghrelin [9,16]. These observations suggest that the phenotypic changes in the vagus may contribute to the development and maintenance of obesity.

High fat feeding induced an inflammatory response including an up-regulation of macrophages and microglia as well as increased inflammatory cytokines in the vagal ganglia and hypothalamus [205]. This inflammatory response may contribute to the blunting of ghrelin signaling in the vagus ganglia [206]. On the other hand, celiac vagotomy reduced high fat diet-induced inflammation in the hypothalamus tissues suggesting that the vagal afferent nerve may transfer gut-delivered inflammatory signals to the hypothalamus [205].

6.3. Vagal CGRP mediates gastric mucosa defense

The gut is densely innervated by vagal sensory afferents containing calcitonin gene-related peptide (CGRP), substance P, vasoactive intestinal polypeptide (VIP) and tachykinins [207,208]. The density of CGRP-immunoreactive fibers in the gastric mucosa was markedly reduced by vagotomy [209]. It was demonstrated that stimulation of afferent nerve by intragastric capsaicin protected gastric mucosa against irritants in the [167–169]. Similarly peripheral administration of CCK also attenuated ethanol-induced mucosal damage, an action abolished by CGRP antagonist, vagotomy or afferent denervation by capsaicin [210] but restored by exogenous administration of CGRP [209–212]. Thus afferent release of neuropeptides such as CGRP may modulate mucosa hemostasis via vagal reflex and paracrine action [169]. The efferent limb involves activation of vagal cholinergic pathway which stimulates the release of mucosal prostaglandin and nitric oxide to regulate blood flow and activation of mast cells [213].

7. Concluding remarks

A high degree of plasticity is required to ensure that vagally-regulated gastrointestinal functions respond appropriately to a variety of intrinsic and extrinsic factors such as feeding, stress and even time of the day. These mechanisms are important for adaptive response and homeostasis. Plastic changes in the vagus also occur in pathophysiological conditions such as obesity and diabetes. These changes may adversely affect gastrointestinal functions. A clear understanding of the molecular and cellular mechanisms mediating these events may provide novel therapeutic targets for prevention and or treatment.

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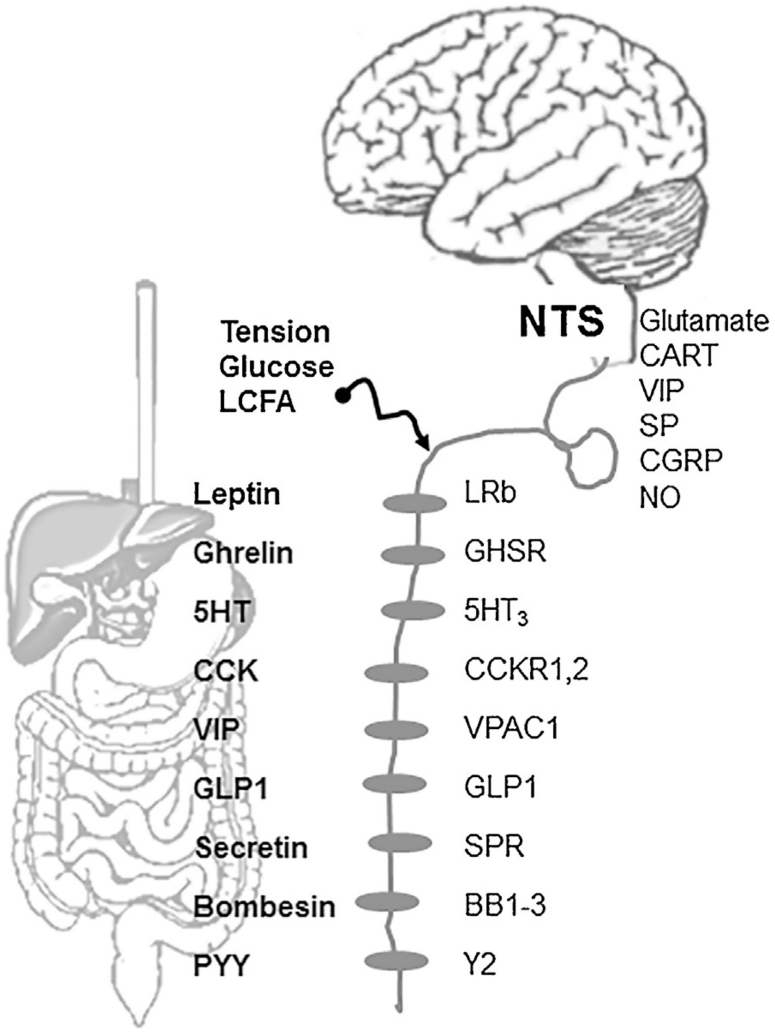

Fig. –.

Vagal afferent signaling is regulated by complex neural, hormonal and mechanical signals. Nutrients trigger the release of gastrointestinal peptides that act on specific receptors on vagal afferents. Vagal afferents synapse with the second order neurons in the NTS by releasing a variety of neurotransmitters which act on higher centers to regulate gastrointestinal functions. $5HT_3$, serotonin receptor; BB1–3, bombesin receptors;CART, cocaine and amphetamine regulated transcript; CCK, cholecystokinin; CCK-1,2, cholecystokinin-1 and 2 type receptor; GHSR, growth hormone secretagogue receptor; GLP-1, glucagon-like peptide-1; GLP1, glucagon-like peptide-1 receptor; LCFA, long-chain fatty acid; LepR, leptin receptor; PYY, peptide YY; Y2-receptor; NO, nitric oxide; NTS, the nucleus of the solitarii tract; SP, substance P; SPR, secretin receptor; VIP, vasoactive intestinal peptide; VPAC1, receptor.

Table 1 –

Gutpeptides and theirroles in gastrointestinal functions

Mediator	Source	Receptor	Vagally mediated function	References
CCK	Intestinal EC I-cells	CCK1 CCK2	Contraction of gallbladder; Pancreatic stimulation; Satiety; Motility; Acid secretion.	[4,54–60]
Leptin	Adiposities; EC Parietal cells	LRb	Inhibition of food intake; mechano-sensitization	[9,16,61,62]
Ghrelin	EC x/A cells in the stomach	GHSR1a	Induces food intake; insulin secretion; gastric acid secretion; gastric emptying, relaxation; intestinal transit; fat tissue metabolism; regulates gene transcription and modulates neural electrical activity	[63–72]
Bombesin	Endocrine cells gastric mucosa	BB1 BB2 BR3	Inhibition of gastric emptying; inhibition of food intake; stimulates gastric acid secretion and gastrin release.	[73–75]
PYY	Small intestine L-cells	Y2	Decrease intragastric tone; inhibit gastric acid secretion	[11,76,77,78]
Secretin	S-cells duodenum	SPR	Stimulates pancreatic bicarbonate secretion; Inhibits gastric acid secretion and gastric motility.	[79,80]
GLP1	Small intestine L-cells Pancreatic A-cells	GLP1	Anorexic signals; Inhibits gastric secretion; reduces ghrelin plasma concentrations.	[81–85]
5HT (serotonin)	EC cells, ENS neurons	$5HT_3$	Stimulates bowel transit; induces nausea and vomiting.	[86–88]
VIP	Duodenum	VPAC1	Inhibits gastric acid secretion.	[89]

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Table 2 –

Vagus afferent neuron neurotransmitters.

Mediator	Vagally mediated function	References
Glutamate	Mediates CCK-induced satiation; Modulates feeding behavior.	[159–161]
CART	Induces satiation	[13,150,162]
VIP	Inhibits gastric acid secretion	[89,163]
SP	Modulate synaptic input to NTS	[164–166]
CGRP	Induces satiety; Gastric mucosa protection	[165,167–169]
NO	Enhances mechano-sensitivity	[170,171]