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Brainstem Neuropeptides and Vagal Protection of the Gastric Mucosal Against Injury: Role of Prostaglandins, Nitric Oxide and Calcitonin-Gene Related Peptide in Capsaicin Afferents

Y. Taché*
CURE: Digestive Diseases Research Center and Center for Neurovisceral Sciences & Women's Health, Digestive Diseases Division, David Geffen School of Medicine at UCLA and VA Greater Los Angeles Healthcare System, Los Angeles, California, USA

Abstract

Earlier experimental studies indicated that the integrity of vagal pathway was required to confer gastric protection against damaging agents. Several peptides located in the brainstem initially identified to influence vagal outflow to the stomach, as assessed by electrophysiological approach or by vagal dependent alterations of gastric secretory and motor function, were investigated for their influence in the vagal regulation of the resistance of the gastric mucosa to injury. Thyrotropin releasing hormone (TRH), or its stable TRH analog, RX-77368, injected at low doses into the cisterna magna or the dorsal motor nucleus (DMN) was the first peptide reported to protect the gastric mucosa against ethanol injury through stimulation of vagal cholinergic pathways, inducing the release of gastric prostaglandins/ nitric oxide (NO) and the recruitment of efferent function of capsaicin sensitive afferent fibers containing calcitonin-gene related peptide (CGRP). Activation of endogenous TRH-TRH_1 receptor signaling located in the brainstem plays a role in adaptive gastric protection against damaging agents. Since then, an expanding number of peptides, namely peptide YY, CGRP, adrenomedullin, amylin, glugacon-like peptide, opioid peptides acting on μ, δ_1 or δ_2 receptors, nocicpetin, nocistatin, ghrelin, leptin and TLQP-21, a peptide derived from VGF prohormone, have been reported to act in the brainstem to afford gastric protection against ethanol injury largely through similar peripheral effectors mechanisms than TRH. Therefore gastric prostaglandins and CGRP/NO pathways represent a common final mechanism through which brain peptides confer vagally mediated gastroprotection against injury. A better understanding of brain circuitries through which these peptides are released will provide new strategies to recruit integrated and multifaceted gastroprotective mechanisms.

Keywords

Adrenomedullin; CGRP; ethanol; ghrelin; nitric oxide; prostaglandins; TRH; vagus

1. INTRODUCTION

The central nervous system has long been alleged to influence the development of gastric erosions. Cushing's clinical report in 1932 established that patients with head injury, cerebral stroke or tumor had a high incidence of gastritis [1]. Thereafter, experimental

*Address correspondence to this author at the CURE: Digestive Diseases Research Center, Building 115, Room 117, VA Greater Los Angeles Healthcare System, 11301 Wilshire Boulevard, Los Angeles, CA 90073, USA; Tel: 310-312-9275; Fax: 1-310-268-4963; ytache@mednet.ucla.edu.

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studies targeted specific brain nuclei by stereotaxic approach to perform electrical lesions or stimulations and identified the limbic, cortical and hypothalamus as areas that have an impact on the development of gastric erosions [2–4], In particular, electrical lesions of the centromedial amygdala and ventroamygdalafugal pathways or electrical stimulation of the medial forebrain bundle-posterior hypothalamus attenuated the incidence and severity of stress-related gastric ulcers [4,5]. Subsequent studies used pharmacological interventions and showed that centrally active drugs including antidepressants, sedatives, hypnotics and antipsychotics protect against stress-related experimental gastric ulcers [6,7]. These initial reports drew the attention onto mechanisms of gastric mucosal defense that can be initiated within specific brain nuclei. They also paved the way to elucidate brain transmitters and neural pathways at play to increase the resistance of the gastric mucosa to injury, along with the peripheral mechanisms involved as effectors within the stomach.

In 1979, we provided the first evidence that peptides act in the brain to protect against the development of gastric erosions induced by cold restraint stress in rats using the 14-amino acid peptide bombesin, derived from the frog skin *Bombina bombina* [8], The underlying mechanisms of the centrally-mediated inhibitory effect of bombesin injected into the cisterna magna were linked with changes in the autonomic nervous system activity leading to the simultaneous inhibition of gastric acid and pepsin secretion and motility while stimulating gastric mucus-alkaline secretion, thereby increasing the resistance of the gastric mucosa [9]. This initial observation opened a new field to investigate the role of neuropeptides in the brain regulation of gastric mucosal defense [10]. During the last few decades, several brain peptides have been identified to act in the brain to alleviate gastric mucosal erosions in different experimental models as well as the key role of the vagus in this brain-gut intereaction [11–14], Peptides injected into the brain at the level of the lateral brain ventricle or cisterna magna conferring significant gastric protection against ethanol-induced gastric mucosal injury include hypothalamic releasing hormones, such as thyrotropin releasing hormone (TRH) [11], corticotropin releasing factor, (CRF) [15], opioid peptides (enkephalins acting through both δ_1 and δ_2 receptors and β-endorphin acting onμ receptor) [16] and related peptides (nociceptin and nocistatin acting on δ, μ and κ receptors) [17], brain-gut peptides influencing food intake, namely peptide YY (PYY) [18], leptin [19], glucagon-like peptide-1 (GLP-1) [20] and ghrelin [21], and members of calcitonin gene-related peptide (CGRP) family, CGRP [22], calcitonin [23], adrenomedullin [24] and amylin [25] and the VGF-derived peptide, TLQP-21 [26].

Administration of peptides into the brain provided relevant physiological tools to assess both the central and peripheral mechanisms involved in brain regulation of gastric mucosal resistance in various models of gastric injury in rodents [12,27]. In particular, early recognition of peptides involved in the brain regulation of gastric secretory and motor function through vagal dependent pathways [28–30], combined with earlier reports that the integrity of the vagus was required for gastric cytoprotection against damaging agents [31,32], provided a strong rationale to examine the gastroprotective action of selective peptides influencing vagal outflow to the stomach. This review will provide insight on central vagal-dependent mechanisms of gastric protection induced by brain neuropeptides with a focus on TRH, PYY, CGRP and related members initially reported in our laboratories along with recent developments in this field.

2. BRAINSTEM TRH AND VAGAL MUSCARINIC GASTRIC PROTECTION

The three amino acid peptide, TRH, was the first isolated hypothalamic releasing hormone and named after its action to induce the release of thyroid-stimulating hormone in the pituitary [33,34]. Soon thereafter, studies revealed that TRH immunoreactivity was also distributed in extrahypothalamic brain sites and that central injection of TRH exerts

pleiotropic actions unrelated to the activation of the hypothalamic-hypophyseal thyroid axis, broadening the repertoire of its biological function [35]. In particular, TRH expressed in the brainstem is well documented to play a key role in the stimulation of the autonomic nervous system [36]. Convergent neuroanatomical and electrophysiological studies showed that TRH acts in the central nervous system to stimulate gastric vagal and adrenal sympathetic efferent activity [36,37] and to induce a vagal cholinergic mediated activation of neurons in gastric myenteric and submucosal plexi in rats [38–40]. TRH-containing nerve fibers and terminals form a dense network within the dorsal vagal complex (DVC; composed of the nucleus tractus solitarius, NTS, dorsal motor nucleus of the vagus, DMN and area postrema, AP) and synapse on dendrites of DMN neurons innervating the stomach in various species [41]. In addition, neuroanatomical tracing, knife cuts and localization of TRH synthesizing neurons ascertained that TRH fibers in the DVC arise exclusively from brainstem nuclei, namely the raphe pallidus, raphe obscurus and the parapyramidal region with no contribution from hypothalamic paraventricular nucleus (PVN) projecting neurons [28,42]. In addition, TRH_1 receptors are localized on DMN neurons [43], where TRH exerts a direct postsynaptic excitatory action [44]. Consistent with the activation of preganglionic motor neurons of the vagus, TRH or the stable TRH analog, RX-77368 injected into the cisterna magna induces a dose-related activation of gastric vagal efferent discharges in rats [37]. Therefore, TRH and stable TRH agonists injected into the brain medulla provide physiologically relevant tools to probe vagal-dependent gastroprotective mechanisms [11,42].

Convergent neuropharmacological and functional studies established that TRH or RX-77368 injected at low doses into the cisterna magna or DMN result in vagal-dependent reduction of gastric mucosal lesions induced by intragastric instillation of concentrated ethanol in conscious or anesthetized rats, which was no longer observed when peptides were injected at higher doses [18,45–51]. In the absence of selective TRH_1 receptor antagonist, intracisternal pretreatment with the antisense oligodeoxynucleotide to the rat TRH_1 receptor was used and found to prevent intracisternal RX-77368 -induced 80% reduction of gastric injury evoked by intragastric administration of ethanol, indicative of a TRH_1 receptor-mediated action of TRH analog on DMN neurons [18]. Subsequent studies were directed to determine whether findings observed with exogenously administered TRH can also be reproduced with endogenous medullary TRH. We examined this contention in a model of adaptive cytoprotection originally discovered by André Robert [52], whereby intragastric instillation of a mild irritant increases the resistance of the gastric mucosa leading to protection against subsequent exposure of the mucosa to stronger irritants through vagal-dependent mechanisms [52]. The injection of TRH antibody bilaterally into the DVC or the cisterna magna prevented the adaptive gastric protection induced by intragastric administration of mild irritants (0.35 N HC1 or 20% ethanol) before that of strong irritants (0.6 N HC1 or 60% ethanol) [53,54]. These data supported the contention that the vagal-dependent gastric adaptive gastric cytoprotection is mediated by endogenous medullary TRH [54], Additional evidence for a gastroprotective action of endogenous TRH in the brain was based on the distribution of cell bodies synthesizing TRH within the ventral medulla, namely the raphe pallidus, raphe obsucurus and parapyramidal region [28]. In these nuclei, preproTRH containing neurons project towards the DVC [28,42] where they provide dense networks of TRH-containing fibers and terminals innervating DMN neurons [55,56]. We demonstrate that the activation of neuronal cell bodies in the raphe pallidus by microinjection of kainic acid at low doses that did not increase gastric acid secretion, dampened gastric lesions induced by intragastric administration of 60% ethanol [54,57]. Site specificity to TRH synthesizing neurons was ascertained by the absence of gastroprotection when kainic acid was microinjected outside of the raphe pallidus [54]. In addition, the microinjection of TRH antibody bilaterally into the DMN abrogates the gastroprotection against 60% ethanol induced by kainic acid microinjected into the raphe pallidus [54]. Therefore these data indicate that the activation of TRH synthesizing neurons in the raphe pallidus-projecting

towards the DVC releases TRH at their terminals in the DVC to influence vagal outflow to the stomach conferring vagal cytoprotection under conditions of mild activation [54, 58]. TRH action can be modulated by other brainstem peptides. We showed a synergistic interaction between the stable TRH agonist, RX-77368 and PYY agonist [Pro^{34}]PYY to confer gastroprotection against ethanol [59]. It is also likely to occur as well between other signaling pathways expressed in the DCV. In particular, recent neuroanatomical and functional studies support an interaction between TRH and leptin in the DVC. TRH_1 and leptin receptors are co-localized on neurons in the DVC including DMN neurons [60] and leptin injected into the cerebrospinal fluid induces vagal dependent gastric protection mediated by similar peripheral mechanisms as the central action of TRH [19,61].

The peripheral effector mechanisms that increase the resistance of the gastric mucosa to chemical injury upon injection of TRH or RX-77368 into the cisterna magna or the DMN at low doses, or by endogenously released TRH in response to the raphe pallidus activation, have been delineated [11,42,62]. Activation of the TRH_1 receptor in the DMN induces a vagal cholinergic dependent increase of transmitters in the gastric mucosa including prostaglandin E_2 (PGE_2) [63] and nitric oxide (NO) [64,65], which contribute to the gastric protection as the NO synthase inhibitor, N^G-nitro-L-arginine methyl ester (L-NAME) and the non selective cylcooxygenase (COX)-l and COX-2 inhibitor, indomethacin, unlike the more selective COX-2 inhibitor, nabumetone, negated the protective effect of intracisternal TRH or TRH analog [45,47–50,54,58]. In addition, TRH injected intracisternally at low doses stimulates gastric splanchnic afferents as demonstrated by electrophysiological recording [66] and activates the local effector function of capsaicin-sensitive splanchnic afferent pathways containing CGRP [46,58]. Capsaicin pretreatment to induce ablation of primary sensory neurons resulting in the depletion of CGRP-containing fibers [67], and pharmacological blockade of peripheral CGRP receptors using $CGRP_{8–37}$ and NO pathway with L-NAME blocked the increased gastric mucosal blood induced by medullary TRH [58,64,68] and gastroprotection [12,46]. This implies that the integrity of sensory fibers containing CGRP and NO mediate the vagal cholinergic increase in gastric mucosal blood flow [68]. Previous investigations established that gastric hyperemia plays a critical role to withstand gastric injury induced by intragastric ethanol [69,70], therefore the stimulation of gastric mucosal blood represents an important mechanism in the protective action of central TRH. Of interest, the vagally mediated gastric prostaglandins released, induced by intracisternal injection of TRH analog at a low dose [45,71], does not contribute to the gastric hyperemia but, along with CGRP, inhibit the vagal stimulation of acid secretion [48,68]. This explains the lack of gastric acid increase observed with low dose TRH analog injected intracisternally despite the stimulated gastric vagal efferent activity [68,72], As initially established by Robert *et al.* [73], the mechanisms of cytoprotection against ethanol-induced gastric injury conferred by prostaglandins are independent of the inhibition of gastric acid secretion. Therefore the PGE_2-dependent components of the gastric cytoprotection induced by central TRH are likely to involve other non gastric hyperemic and antisecretory mechanisms that may include the opening of K_{ATP} channels and/or suppression of inflammatory mediators and reactive oxygen metabolites reported to be involved in prostaglandins-mediated gastric mucosal defense [74,75]. Whether gastric PGE_2 released by central vagal activation interacts with an EP_1 receptor subtype, characterized to mediate gastric cytoprotection and adaptive gastric protection, is still to be examined [76]. Of interest, additional mechanisms may also contribute to the gastroprotective response such as the vagal cholinergic release of ghrelin from X/A endocrine cells located in the gastric mucosa [77]. Recent reports showed that intracisternal injection of TRH or endogenous TRH released by a short cold exposure markedly increased plasma levels of ghrelin through activation of vagal cholinergic pathways [78,79]. This combined with evidence that peripheral ghrelin protects against gastric lesions induced by ethanol [80] support this contention that remains to be demonstrated.

We previously identified that the activation of medullary TRH_1 receptor contributes to the cephalic phase of gastric digestion associated with submaximal vagal stimulation [81,82], We can therefore speculate that the cephalic phase, through activation of medullary TRH, also triggers these gastric mucosal protective mechanisms. Conversely, a deficient cephalic phase may render the gastric mucosa more vulnerable to aggressive factors in the absence of such vagally recruited protective mechanisms.

3. PYY IN THE DORSAL VAGAL COMPLEX AND VAGAL CHOLINERGIC GASTRIC PROTECTION

The NPY family includes NPY and two other related peptides, PYY and pancreatic polypeptide (PP). NPY is one of the most abundant peptides found in the brain [83] while PYY and PP are localized in the endocrine cells of the gut [84]. PYY and PP are released after a meal and exert central actions through binding on Y receptors located outside the blood brain barrier, namely in the AP [85]. Recent studies also identified PYY synthesizing neurons in the brain, selectively in the gitantocellular reticular nucleus in various species with abundant projecting fibers to the DVC [86]. Topographical differences between PYY and NPY terminal fields in the DVC have recently been characterized. There is a more dense representation of NPY in the DMN than PYY that has the highest density of fibers in the dorsal and lateral NTS while NPY fibers are concentrated in the medial NTS [86]. NPY and related peptides interact with NPY receptors that belong to the seven transmembrane G-protein coupled receptor family (subfamily type I). The four cloned receptor subtypes have been designed Y_1, Y_2, Y_4 and Y_5 and a PYY-preferring receptor has been characterized by pharmacological analysis [83]. Autoradiographic studies have localized Y_1, Y_2 Y_4 and Y_5 receptors [87,88] along with an atypical Y receptor subtype [89] in all structures of the DVC.

Based on our previous studies showing that rat/porcine PYY micro injected into the DMN stimulated gastric acid secretion through vagal cholinergic-dependent pathways [90,91], we investigated whether central rat/porcine PYY influences the development of experimental gastric erosion to extend the concept of central vagal-dependent gastric protection. Using doses of PYY subthreshold to stimulate gastric acid secretion, we established a centrally mediated dose-related protection against ethanol-induced gastric lesions in urethane anesthetized rats [18,59,92]. Then we used a pharmacological approach to get insight to the Y receptor subtypes involved. Peptide gastroprotective action against ethanol was mimicked by the intracisternal injection of PYY analog, [Pro^{34}]PYY (Y_1,/PYY preferring) while rat NPY ($Y_1/Y_2/Y_5$ agonist), rat PP (Y_4 agonist), rat $PYY_{3–36}$ (Y_2/Y_5 agonist), and [Leu^{31}, Pro^{34}] NPY ($Y_1/Y_5/Y_4$ agonist) had no effect when tested under the same conditions [59]. Based on the reported receptor binding affinities of NPY/PYY/PP and peptide analogs on rat Y receptor subtypes, the centrally-mediated PYY gastroprotective action does not seem to be mediated by current pharmacologically established Y_1, Y_2, Y_4 and Y_5 receptors and may involve a PYY-preferring receptor [59]. This is in keeping with binding studies supporting the existence of an atypical Y receptor subtype in the DVC that is insensitive to Y_1, Y_2, Y_4 and Y_5 receptor blockers [88,89]. Intracisternal pretreatment with the TRH_1 antisense oligodeoxynucleotide did not alter the gastroprotective action of PYY against intragastric ethanol under conditions that prevented the gastroprotective effect of intracisternal TRH analog [18]. Therefore PYY action is not secondary to TRH release or activation of medullary TRH_1 receptor in the DVC [18]. However, there is a synergistic effect between intracisternal RX-77368 and PYY or [Pro^{34}]PYY [18,59]. These data point towards independent peptidergic pathways in the brainstem that can be activated by different peptides to convey gastric protection against injury.

Studies on the peripheral mechanisms of PYY action indicate that gastric prostaglandins do not play a primary role while vagal cholinergic CGRP/NO signaling pathways are involved. This was established by the blockade of PYY action by peripheral administration of atropine, L-NAME and CGRP receptor antagonist while indomethacin had no effect [18]. The lack of prostaglandin involvement in intracisternal PYY-induced gastric protection against ethanol, while prostaglandins play a role in that of TRH, further supports the notion that PYY does not act by recruiting medullary TRH. Activation of CGRP/NO enhances the resistance of the gastric mucosa to injury through vascular dependent and independent cellular actions [93,94].

The physiological significance of these observations is still to be defined. However, based on the evidence that PYY can relay information to the DVC by both neuronal [86] and humoral [85,95] pathways and that Y receptor subtypes are expressed in the DVC and regulated by feeding status [88], it may be speculated that PYY may have relevance to integrate feeding status and gastric protection. In particular, intracisternal PYY was shown to have an additive effect with medullary TRH [91]. The co-release of these peptides during cephalic phase (TRH) and feeding (PYY) may promote protective mechanisms in the gastric mucosa.

4. CALCITONIN AND RELATED PEPTIDES: CENTRAL ACTIONS TO PROTECT AGAINST GASTRIC EROSIONS

Calcitonin was originally isolated as a 32-amino acid peptide hormone essential for calcium balance [96]. Now the calcitonin family of peptides encompasses five additional members: two CGRP isoforms, α-CGRP and β-CGRP, adrenomedullin (AM), amylin (AMY) and more recently, intermedin also named adrenomedullin 2 [97–99]. These peptides exert their biological actions in the central nervous system through interaction with the Class II family of G-protein coupled receptors, the calcitonin (CT) receptor and calcitonin receptor-like (CL) receptor. However, CL receptor is a non-functional receptor that requires receptor activity modifying proteins (RAMPs) to confer ligand specificity and induce signal transduction [97]. The functional $CGRP_1$ receptor is composed of CL receptor, coexpressed with the single transmembrane domain protein RAMP1 and the intracellular coupling protein called receptor-component protein (RCP) [97,100,101]. In addition to responding to CGRP, CL receptor functions as an adrenomedullin receptor when it is co-expressed with RAMP2 (AM_1 receptor subtype) and RAMP3 (AM_2 receptor subtype) along with the RCP to facilitate the efficient coupling of AM receptors to G protein-mediated signal transduction [97,100,102]. Similarly, CT receptor in presence of RAMP1, RAMP2 or RAMP3, exhibits high affinity for amylin to generate different amylin receptor phenotypes, $AMY_{1,}$ AMY_2 and AMY_3 respectively [83,101,103]. Intermedin/AM_2 can act through the existing CGRP and AM receptors as well as AMY1 and AMY3 receptors and among those, the highest affinity is observed for binding to the AM_2 receptor, although there is also pharmacological evidence suggesting that intermedin/AM_2 might activate receptors which are distinct from the CL and CT receptor complexes [99].

We initially reported that salmon calcitonin, injected intracisternally, dose-dependently prevented gastric lesions produced by high levels of the vagal stimulation or aspirin and by vagal-dependent duodenal lesions evoked by cysteamine [23,104]. By contrast, gastric lesions induced by gastric irritants, such as 40–50% ethanol and 0.6 N HC1, were increased or not changed by calcitonin injected intracisternally or into the lateral brain ventricle [23,105]. Calcitonin action to prevent stress- and aspirin-induced gastric lesions is centrally mediated and more potent than that of other peptides injected into the cerebrospinal fluid such as bombesin, neurotensin and opioid peptides [23]. Brain sites responsive to calcitonin to suppress cold restraint stress-induced gastric mucosa lesions were identified in the lateral,

ventromedial hypothalamus and PVN [106], consistent with intense expression of CT receptors in these hypothalamic nuclei [107]. By contrast, extrahypothalamic sites, namely the caudate putamen, cerebral cortex or hippocampus were ineffective [106]. Peripheral mechanisms through which central calcitonin prevents gastric erosions induced by stress in rats may involve the associated inhibition of gastric acid secretion, motility and the increase of gastric mucus secretion [23,106], as well as duodenal prostaglandin generation in the cysteamine model [104].

α-CGRP is a 37-amino acid peptide encoded by alternative splicing of the calcitonin gene that shares nearly 25% homology with calcitonin [108]. The peptide injected into the cisterna magna prevented gastric lesions induced by high levels of central vagal stimulations [22]. Three-dimension reconstruction showed CGRP immunoreactive fibers in the NTS in close proximity of dendrites or somata of identified gastric efferent motor neurons [109]. Immunoreactivity for RCP used as a marker to localize CGRP receptors is also present in neurons of the DMN [110]. These data suggest that CGRP released at this site may influence the activity of preganglionic vagal motor neurons. This is corroborated by electrophysiological evidence that ic injection of α-CGRP decreases gastric vagal efferent discharges [22] and inhibits gastric acid secretion through vagal-dependent mechanisms [111]. Consistent with vagal-dependent mechanisms being involved in gastroprotection against local gastric irritants, we showed that intracisternal injection of α-CGRP dose-dependently suppressed gastric erosions induced by intragastric administration of 40% or 70% ethanol in rats [22,24]. α-CGRP cytoprotective action was prevented by the intracisternal injection of the $CGRP_1$ receptor antagonist, CGRP8–37 [24], suggesting an interaction with the $CGRP_1$ receptor complex, CL/RAMP1/RCP that has high affinity for CGRP and $CGRP_{8–37}$ and no affinity for calcitonin [83]. A distinct involvement of $CGRP_1$ and CT receptors is also supported by functional studies showing that intracisternal injection calcitonin aggravates gastric lesions induced by 40% ethanol while under the same conditions, α-CGRP exerts a protective effect [22,23]. The mechanisms of gastric cytoprotection against ethanol induced by intracisternal α-CGRP are not indomethacin sensitive, not related to the antisecretory effects and may involve increase in gastric mucosal blood flow and other mechanisms to be elucidated [22].

Adrenomedullin is a 52-amino acid which has a 25–30% sequence homology with CGRP [112]. When injected intracisternally adrenomedullin dose-dependently suppresses gastric lesions induced by 70% ethanol. By contrast when injected intravenously at twice the effective intracisternal dose, the peptide did not alter ethanol-induced gastric lesions, showing that adrenomedullin action is initiated in the brain [24]. The $CGRP_1$ receptor antagonist, $CGRP_{8–37}$ injected intracisternally did not prevent the gastroprotective effect of adrenomedullin while inhibiting that of α-CGRP tested under the same conditions [24]. This suggests that adrenomedullin does not interact with CGRP receptor complex but is likely to activate its own adrenomedullin receptors [24]. The central action of adrenomedullin is mediated by vagal cholinergic-dependent mechanisms that involve prostaglandins and NO since subdiaphragmatic vagotomy, peripheral injection of atropine, indomethacin and NO synthase inhibitor blocked the cytoprotective action of adrenomedullin [24]. The fact that intracisternal adrenomedullin cytoprotective action is abolished by indomethacin [24], unlike that of intracisternal CGRP [22], further supports the contention that these related peptides act through distinct receptors recruiting different peripheral protective mechanisms. Mapping of RAMP2 and CL, components conferring adrenomedullin receptor specificity, showed that they are expressed in numerous autonomic centers including the area postrema, NTS and DMN [113], providing anatomical support to the vagal-dependent gastric cytoprotection induced by adrenomedullin injected into the cisterna magna [24]. The central vagally mediated gastroprotective action of adreuomedullin contrasts with most of the other

visceral responses induced by the peptide injected into the brain, which have been mainly related to the central stimulation of sympathetic activity [114].

The physiological significance of brain adrenomedullin is still to be established. However preproadrenomedullin and adrenomedullin immunoreactivity are present in a number of autonomic nuclei in the brain such as the PVN, central nucleus of the amygdala, arcuate nucleus and NTS [114–116], known to influence vagal outflow to the stomach [117]. This suggests that adrenomedullin is produced by and can also act at these medullary nuclei regulating vagal outflow to the stomach or hypothalamic or limbic nuclei projecting to the DVC [118,119]. The phenotype of knockout mice with selective brain depletion of adrenomedullin is consistent with a role of the peptide to maintain homeostasis both under normal and stress conditions [120]. This points to a potential adaptive influence of adrenomedullin in the brain to maintain the gastric mucosa under conditions that threaten its integrity.

Amylin is a 37-amino acid peptide that shares 45% structural homology to CGRP and weaker homology with adrenomedullin (23%) and mammalian calcitonin (less than 20%) [97]. The peptide injected into the lateral brain ventricle dose-dependently prevents ethanol-induced gastric lesions while amylin injected peripherally or intracerebroventricularly after the onset of ethanol injury was ineffective [105,121]. The central action of the peptide was unrelated to its gastric antisecretory activity and abolished by peripheral administration of indomethacin, L-NAME and depletion of sulfhydryl groups [105,121]. These data indicate that central amylin induced gastric protection against ethanol through NO, prostaglandin and endogenous sulfhydryl mechanisms. Recent studies identified dense amylin binding sites and amylin immunoreactive nerve fiber networks in the NTS and DMN with fibers reaching the AP [122,123]. While a physiological implication of hindbrain amylin signaling pathways has been established in the inhibition of food intake [124], the role of brain amylin in increasing gastric protective mechanisms is still to be delineated.

5. SUMMARY

We reviewed the central actions of specific brain peptides that early on were reported to protect the gastric mucosa from injury gastric irritants such as ethanol (Table 1). Brain medullary TRH is the only brain peptide established thus far to play a physiological role in the vagal regulation of the resistance of the gastric mucosa to injury. This was determined by convergent sets of neuroanatomical studies regarding the pattern of TRH_1 receptors and ligand distribution in the DVC and electrophysiological, neuropharmacological and functional studies. Brain medullary TRH or a low dose of exogenous TRH or its stable TRH analog, RX-77368 stimulates the release of several peripheral signaling molecules (prostaglandins, NO, CGRP, ghrelin) through vagal cholinergic pathways [11,42] (Table 2). The gastroprotective action against ethanol-induced gastric injury induced by these vagally released peripheral transmitters is brought about by the increased in gastric mucosal blood flow elicited by the vagal cholinergic release of CGRP and NO and other intracellular protective mechanisms through which prostaglandins protect the gastric mucosa [125].

Central injection of TRH at various doses to trigger different levels of vagal activation unmasked the ability of low levels of vagal efferent activity to confer increased resistance of the gastric mucosa to withstand gastric mucosal irritants such as ethanol and proved a useful tool to delineate the underlying mechanisms of vagal dependent protection and damage to the gastric mucosa [62]. These initial reports have paved the way early to key vagal-dependent gastric effectors simultaneously activated, namely gastric prostaglandins and/or CGRP-NO signaling pathways [45–47]. Now CGRP-NO alone or in conjunction with prostraglandins are established to serve as common final peripheral effector mechanisms

induced by several brain peptides to withstand the gastric damaging effect of ethanol as exemplified in addition of TRH, δ_1, δ_2, or μ receptor agonists, [16], nociceptin [17,126], VGF-derived peptide, TPQP-21 [26], amylin [105,121], ghrelin [21,80,127,128] and leptin [19,61] (Table 2).

Collectively existing knowledge so far has established that there are several peptides acting on their cognate receptors in the brain prominently expressed at the level of the DVC to induce receptor specific mediated increased resistance of gastric mucosa to deleterious agents. It may be speculated that the redundancy of brain peptides may be linked with different pathophysiological conditions whereby they are recruited into the brain under stress, feeding or damage of the gastric mucosa. While distinct peptidergic pathways acting singly or in synergy are recruited in the brain, they converge toward common neural effector mechanisms involving vagal dependent recruitment of gastric prostaglandins-CGRP-NO mechanisms (Table 2). It is likely that a better understanding of the central vagal mechanisms through which brain-gut peptides activate peripheral gastroprotective transmitters, such as prostaglandins and CGRP/NO pathways, along with central mechanisms that triggers the release of these peptides in the brain, will provide new strategies to integrate gastric secretory, motor and vascular responses that promote the increased resistance of the gastric mucosa to injuries.

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Table 1

Gastric Protection Against Ethanol-Induced Mucosal Lesions by Central Injection of TRH Analog, RX-77368, FYY and CGRP-Related Peptides

Peptides	Dose (pmol/rat)	Route	Gastric Ethanol %	Gastric Protection %	References
RX-77368	7–26	DMN	60%	79–61%	[49]
RX-77368	3.8	ic	60%	78–88%	[46,47]
RX-77368	2.5–3.8	ic	60%	58–78%	[45]
RX-77368	1.5	DVC	60%	57%	[51]
RX-77368	25–38	ic	60%	43–77%	[50]
RX-77368	4	ic	45%	59%	[18]
TRH	19	ic	60%	63%	[48]
PYY	23–117	ic	45%	27–63%	[18,92]
PYY+RX-77368	6+2	ic	45%	44%	[18]
[Pro^{34}]PYY	12–120	ic	45%	30–75%	[59]
[Pro^{34}]PYY+RX-77368	6+2	ic+ic	45%	43%	[59]
α-CGRP	8–80	ic	40%	76–97%	[22]
α-CGRP	150	ic	70%	76%	[24]
Adrenomedullin	75–150	ic	70%	42–70%	[24]
Amylin	169–560	icv	50%	50–60%	[105,121]
Calcitonin	28	ic	40%	0%	[23]
Calcitonin	28–550	icv	50%	0%	[105]

DMN: dorsal motor nucleus of the vagus; DVC: dorsal vagal complex; ic: intracisternal; icv: intracerebroventricular.

Table 2

Central Injection of Neuropeptides-Induced Gastric Mucosal Protection Against Intragastric Administration of Ethanol in Rats: Peripheral Mechanisms

Peptides	Route	Vag-X	Atropine*	Indo*	Capsaicin*	$CGRP_{8-37}$*	L-NAME*	References
TRH/RX-77368	DMN, ic	Block	Block	Block	Block	Block	Block	[45–50]
PYY/Pro^{34}PYY	ic	-	Block	No	--	Block	Block	[18]
Adrenomedullin	ic	Block	Block	Block	--	Block	Block	[24]
Amylin	icv	--	--	Block	--	--	Block	[105,121]
CGRP	ic	--	--	No	--	--	--	[22]
TLQP-21**	icv	--	Block	Block	Block	--	Block	[26]
Nociceptin	icv	Block	Block	--	Block	Block	Block	[17,126]
Nocistatin	icv, ic	Block	--	Block	--	--	--	[17]
β-Endorphin	icv, ic	Block	--	Block	--	--	Block	[16,129]
δ_1 ag DPDPE	icv, ic	Block	--	Block	--	--	Block	[16,129]
δ_2 ag deltorphin	icv, ic	Block	--	Block	--	--	Block	[16,129]
μ ago, DAGO	icv, ic	Block	--	Block	--	--	Block	[16,129]
Ghrelin	icv	=Block	--	--	Block	Block	Block	[127,128]
GLP-1	icv	Block	Block	--	--	--	Block	[21,80]
Leptin	icv	Block	--		Block	Block	Block	[20] [19]

*Peripheral administration;

**VGF prohormone$_{556–576}$; Ag: agonist; DMN: dorsal motor nucleus of the vagus; ic: intracisternal; icv: intracerebroventricular; Indo: indomethacin; vag-X: vagotomy; -- : not investigated.

Role of vagal cholinergic pathways, nitric oxide, prostaglandins and CGRP releases from capsaisin sensitive fibers assessed using vagotomy and peripheral injection of muscarinic antagonist, atropine, nitric oxide synthase blockade with L-NAME, prostaglandins inhibition with indomethacin and ablation of sensory afferents with capsaicin and blockade of CGRP signaling with CGRP antagonist, $CGRP_{8–37}$ respectively.