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Central and peripheral regulation of gastric acid secretion by peptide YY

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Abstract

Peptide YY (PYY) released postprandially from the ileum and colon displays a potent inhibition of cephalic and gastric phases of gastric acid secretion through both central and peripheral mechanisms. To modulate vagal regulation of gastric functions, circulating PYY enters the brain through the area postrema and the nucleus of the solitary tract, where it exerts a stimulatory action through PYY-preferring Y1-like receptors, and an inhibitory action through Y2 receptors. In the gastric mucosa, PYY binds to Y1 receptors in the enterochromaffin-like cells to inhibit gastrin-stimulated histamine release and calcium signaling via a pertussis toxin-sensitive pathway.

1. Introduction

Peptide YY (PYY) is a 36-amino acid hormone that is structurally and functionally related to neuropeptide Y (NPY) and pancreatic polypeptide (PP) [84]. PYY was originally isolated from the pig intestine [82] and its immunoreactivity has been localized in the open-ended L-type endocrine cells of the terminal ileum and colon in the rat, dog and human [3,20,47]. PYY is released postprandially via extramural neural or endocrine mechanisms which originate in the foregut [28] and by intraluminal nutrients [1,4, 27,83,106], while the basal release of PYY seems to be partly regulated by tonic vagal activity [74,77]. $PYY_{1–36}$ and $PYY_{3–36}$ are the two molecular forms of PYY abundant in the blood [25]. The PYY derivatives [Leu^{31}, Pro^{34}] PYY (or Pro^{34}PYY) and $PYY_{3–36}$ (or $PYY_{13–36}$) show selective affinity to Y1 and Y2 receptors respectively [6]. Circulating PYY displays a profound inhibitory action on gut motility, gastric emptying and acid secretion as well as pancreatic exocrine secretion [32,62,64,65]. This review focuses on the PYY regulation of gastric acid secretion, especially recent findings that reveal PYY actions in the medullary vagal regulatory nuclei and in gastric mucosal enterochromaffin-like (ECL) cells.

2. PYY is a potent inhibitor of gastric acid secretion

Intravenous (iv) infusion of PYY in healthy human volunteers at doses of 0.59 and 0.20 pmol/kg/min significantly suppressed gastric acid and pepsin output during background stimulation with pentagastrin [2]. PYY iv infusion at 0.20 pmol/kg/min increased plasma PYY levels by 27 ± 2 fmol/ml and reduced the incremental gastric volume, acid and pepsin responses to pentagastrin by 90%, 77% and 96% respectively [2]. This study indicates that PYY concentrations in the circulation similar to those seen after food ingestion caused a marked reduction in gastric secretion. Likewise, PYY iv infusion at 400 pmol/kg/h significantly inhibited liver extract (15%) meal-induced gastric acid secretion by 35% in dogs [63]. The inhibitory action of iv infused PYY on gastric acid secretion has also been observed in cats [5], rabbits [51] and rats [36,91] in various acid-stimulatory models. These include acid secretion stimulated by pentagastrin [5], or those stimulated via the mediation of central-vagal activation, such as acid secretion induced by iv insulin [51], subcutaneous (sc) baclofen [36] or intracisternal (ic) injection of thyrotropin-releasing hormone (TRH) analog [91].

The inhibitory action of PYY on gastric acid secretion is interactive with other postprandially released gastrointestinal hormones. Glucagon-like peptide-1 (GLP-1)- (7–36) amide is colocalized with PYY in the L-cell of the ileal mucosa. In dogs, intraduodenal administration of a 10% fat emulsion increased plasma levels of GLP-1 and PYY by

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44 ± 5 and 46 ± 4 fmol/ml respectively and suppressed gastric acid secretion-induced by duodenal perfusion of peptone by 72 ± 4% [22]. Intravenous infusion of GLP-1 or PYY at the dose of 50 pmol/kg/h, which reproduced plasma elevations of these peptides equivalent to that induced by intraduodenal fat, inhibited gastric acid secretion by 66 ± 5% and 51 ± 6% respectively. When GLP-1 and PYY were co-infused the gastric acid secretion was abolished [22]. In human, GLP-1 and PYY are potent inhibitors on sham feeding-induced gastric acid secretion [88]. The additive type of inhibition by postprandial levels of GLP-1 and PYY was also observed with pentagastrin-stimulated gastric acid secretion in human volunteers [87].

Secretin is another inhibitory hormone regulating gastric acid secretion [50,101]. In conscious dogs, pentagastrin-stimulated gastric acid output was inhibited either by iv infusion of secretin or by intraduodenal administration of hydrochloric acid. These inhibitions were further augmented by iv PYY infusion by 32% and 40% respectively, while the mean integrated release of secretin response to duodenal acidification was not affected by PYY [52]. In healthy human volunteers, secretin (0.05 CU/kg/h) and PYY (10 pmol/kg/h) inhibited gastric acid output-stimulated by pentagastrin by 25 and 21% respectively when given alone, and by 38% when combined [61]. These studies demonstrate that PYY interacts with exogenous secretin as well as endogenous secretin released by duodenal acidification in an additive fashion to inhibit pentagastrin-stimulated gastric acid secretion.

The additive interplay of PYY with GLP-1 and secretion indicates that PYY inhibits gastric acid secretion through separate mechanisms from those of GLP-1 and secretion.

3. PYY is more potent to inhibit gastric acid secretion induced by central-vagal stimulation than that induced by peripherally acting secretogogues

In their pioneer studies, Pappas et al. [65] observed in dogs that iv infusion of PYY at 400 pmol/kg/h, a dose that increased blood PYY to levels similar to that observed after intestinal perfusion with oleic acid and significantly inhibited meal-stimulated acid secretion [64], markedly inhibited by 90% the gastric acid secretory response to sham feeding. In contrast, the same dose of PYY only maximally inhibited histamine- and pentagastrin-stimulated acid secretion by 28% and 17% respectively, while had no effect on bethanechol-stimulated acid secretion [65]. These studies demonstrate that PYY virtually abolishes cephalic phase acid secretion while having little, if any, effect on the acid secretory response to exogenous secretogogues. It was speculated that PYY acts by inhibiting acetylcholine release from vagal nerve fibers rather than by inhibiting acetylcholine's action on the parietal cell [65]. Experiments using 2-deoxyglucose (2-DG)-induced acid secretion model showed similar results supporting the inhibitory action of iv PYY on cephalic phase acid secretion [17,32].

The viewpoint of Pappas et al. [65] was further confirmed by later studies in dogs [30] and rats [35]. In fasted rats, administration of PYY (3.2 nmol/kg/h, iv) had no effect on bethanechol-induced acid output, however, it inhibited baclofen-induced acid output by 61.8%, which was more potent compared with the inhibition on pentagastrin- and histamine-induced acid output [35,36]. Baclofen is a γ-aminobutyric acid (B) receptor agonist, which stimulates gastric acid output that could be completely abolished by atropine sulfate or truncal vagotomy [35]. Hashimoto et al. [36] provided more direct evidence showing that PYY inhibited acetylcholine release evoked by electrical transmural stimulation from cholinergic nerve endings of gastric body by 47%. The involvement of the vagus nerve in mediating PYY inhibition of gastric acid secretion has been studied in dogs [50]. The threshold dose of iv PYY to inhibit intragastric peptone meal-induced gastric acid secretion was 5 pmol/kg/h, which was increased to 200 pmol/kg/h after highly selective vagotomy (HSV). The PYY dose producing 50% acid inhibition (ID50) was 128 pmol/kg/h before the HSV. However, after the HSV, the PYY dose that caused a maximal inhibition (90%) in intact animals (500 pmol/kg/h) failed to inhibit acid output by more than 50%. These experiments indicate that PYY inhibits gastric acid secretion in large part through vagal innervation of the gastric fundus [50].

4. PYY acts in the medullary vagal related nuclei to regulate gastric acid secretion

The observations that PYY is a potent inhibitor on cephalic phase acid secretion [36,65] and the inhibition is vagally dependent [50] suggest that the inhibitory effect of PYY on gastric acid secretion is neurally mediated, especially involving the vagus nerve. Recent studies revealed that PYY acts in the medullary dorsal vagal complex (DVC) to modulate gastric functions [11,12,13,14,90,92,95]. Both inhibitory and excitatory actions of PYY were observed. The opposite effects relate with the receptor subtypes involved in a particular action and the PYY doses applied.

4.1. Circulating PYY binds to the dorsal vagal complex (DVC) and area postrema (AP), and activates DVC and AP cells

In the brainstem, the DVC, composed of the dorsal motor nucleus of the vagus (DMN) and the nucleus tractus solitarii (NTS), and the area postrema (AP) are located close to the surface of the 4th ventricle (Fig. 1). These nuclei are of particular importance for central regulation of digestive functions [53] and are potentially important to our understanding of the mechanisms of the gastric regulatory actions of PYY. The DMN contains the motor neuron cell bodies

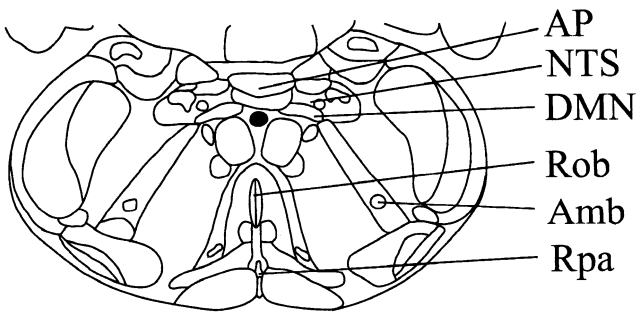

Fig. 1. Coronal brainstem section (interaural-4.68) adapted from the atles of Paxinos and Watson [68] showing the locations of the dorsal motor nucleurs of the vagus (DMN), the nucleus tractus solitarii (NTS), the area postrema (AP), the raphe pallidus (Rpa), the raphe obscurus (Rob), and the nucleus ambiguus (Amb).

from which vagal efferents arise and is the main source of the vagus nerve innervating the stomach, while the NTS receives vagal afferent projections [53]. A number of NTS neurons directly connect with vagal motor neurons in the DMN, forming the vago-vagal reflex, which may result in increased [49,85] or decreased [57] vagal efferent activities. The AP and portions of the NTS are defined as circumventricular organs in that the blood-brain barrier is incomplete [21,29,66]. These regions can therefore act as portals of entry for circulating peptide hormones.

PYY binding sites are presented in the AP and DVC [54]. Specific binding sites for both ^{125}I-[Leu^{31,} Pro^{34}]PYY (Y1 agonist) and ^{125}I-PYY$_{3–36}$ (Y2 agonist) have been detected in the NTS and AP [18]. A recent study revealed that Y1, Y2 and Y4 receptor subtype mRNAs are located in the AP, NTS and DMN [67]. The expressions in the AP and DMN are particularly strong [67]. In intact rats, after iv injection of ^{125}I-labeled PYY to produce a blood concentration of PYY within a range seen after a meal, significant storable binding was observed in the region of the brainstem containing the DVC [37]. The activation of NTS and AP cells by PYY from circulation was showed by the observation that after intraperitoneal (ip) injection of PYY, the expression of Fos, the nuclear protein that is used as a marker of cellular activation [59], was significantly inducted in the DVC and AP [7]. These studies provide morphologic evidence supporting the central actions of PYY.

4.2. Peripheral PYY inhibits central vagally stimulated gastric acid secretion by acting in the brain

The central mediation of peripheral PYY-induced inhibition of vagally stimulated gastric acid secretion has been studied in urethane-anesthetized rats using immunoneutralization with a PYY polyclonal antibody, produced by the Antibody Core in the Center for Ulcer Research and Education (CURE), UCLA [91]. Gastric acid secretion was stimulated by injection into the cisterna magna of a stable TRH analog, which is well established to act on DMN vagal

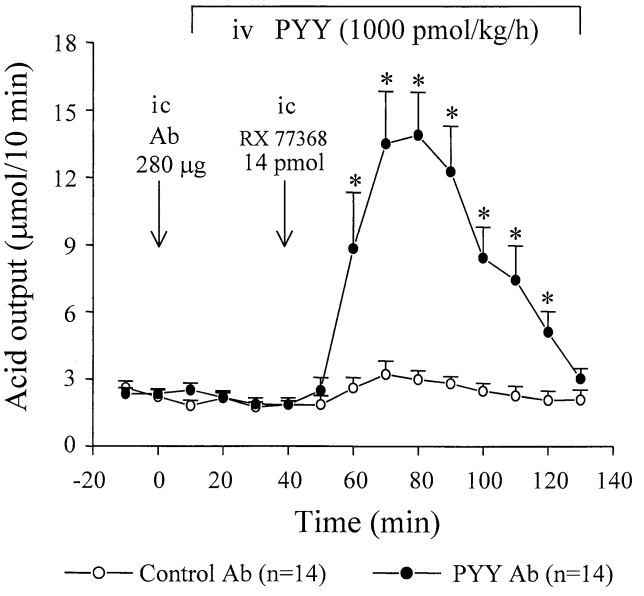

Fig. 2. PYY antibody injected intracisternally (ic) prevented iv PYY-induced inhibition of acid response to ic TRH analog in urethane-anesthetized rats. Each point represents the Mean ± SE of number of rats indicated in parentheses. * $P < 0.05$ compared with control antibody (normal rabbit IgG) ic pretreated group. Adapted from Reference [91].

motor neurons and induces gastric acid secretion through vagal efferent activation [60,78,79]. PYY iv infusion at 250, 500 and 1000 pmol/kg/h dose-dependently inhibited by 52%, 69% and 83% of the acid secretion induced by ic TRH analog. PYY or PYY$_{3–36}$ injected ic at the dose of 2.4 pmol/rat also inhibited the acid response to ic TRH analog by 73% and 80% respectively. Pretreatment with the PYY antibody (4.5 mg/rat, iv), which shows a 35% cross-reaction with PYY$_{3–36}$ by radioimmunoassay, completely prevented the inhibitory effect of iv infused PYY (1000 pmol/kg/h). When injected ic, the PYY antibody (280 μg/rat) reversed not only the inhibition of gastric acid secretion by ic PYY (2.4 pmol) by 64%, but also the inhibition by iv PYY infusion (1000 pmol/kg/h) by 94% (Fig. 2). These results strongly indicate that peripheral PYY inhibits central-vagally stimulated gastric acid secretion through its action at the brain and this action may involve Y2 receptors [91]. The recent finding demonstrating the strong expression of Y2 receptor mRNA in the AP and NTS [67] supports this view.

4.3. PYY inhibits activities of DMN neurons via Y2 receptors

Chen and Rogers [12] studied the action of PYY on DMN neurons using both in vivo and in vitro models. In vivo extracellular recording of single-unit electrical activity of DMN neurons was performed in urethane-anesthetized rats. The gastric-related neurons in the DMN were identified by gastric inflation. PYY or PYY$_{13–36}$ was pressure-injected from a pipette array at 0.25 fmol/cell. Of the identified DMN neurons, 50% were inhibited, 44% were unaffected

and 6% were activated by PYY or $PYY_{13–36}$. The in vitro studies were performed using coronal brainstem sections of 400 μm thickness. Extracellular single unit recordings provided similar results as that observed in the in vivo preparations. PYY or $PYY_{13–36}$ inhibited 50%, left unaffected 42% and activated 7% of DMN neurons under both normal and blockade media (high-Mg^{2+}/low-Ca^{2+}) conditions. These results showed that PYY and Y2 agonist peptide exert a predominantly inhibitory effect on DMN cells in normal in vivo and in vitro conditions as well as in an in vitro model with synaptic blockade. The inhibitory effect recorded under high-Mg^{2+}/low-Ca^{2+} condition suggests that the PYY effects on the DMN neurons are direct and not mediated by synaptic inputs from other neurons [12]. Functional studies on gastric motility by the same research group have revealed that PYY or $PYY_{13–36}$ microinjected into the DVC at doses ranging from 2 to 20 fmol significantly inhibited gastric motility induced by centrally applied TRH, while in a higher dose (2 pmol) PYY displayed a excitatory effect on basal gastric motility [11,14].

4.4 PYY acts in the DVC to induce vagally mediated stimulation of gastric acid secretion and gastric protection through PYY preferring, Y1-like receptors

In contrast to the inhibition on gastric motility induced by low doses of PYY (2–20 fmol/rat) in the DVC, PYY microinjected into the DVC with higher doses induced dose-dependent and site specific stimulation of gastric acid secretion [95]. The mean basal gastric acid secretion in urethane-anesthetized rats was 1.7 μmol/10 min. After PYY was unilaterally microinjected into the DVC at doses of 7, 12, 24 and 47 pmol, the net increase in gastric acid output were 13, 22, 40 and 59 μmol/10 min, respectively [95]. Bilateral cervical vagotomy completely abolished the acid response to PYY (47 pmol) microinjected into the DVC. The PYY stimulatory effect in the DVC was potentiated by co-injection of PYY with either TRH or serotonin receptor (5-HT_2) agonist [95]. TRH and serotonin are the two natural neurotransmitters synthesized in the raphe nuclei and released from nerve terminals innervating the DMN to modulate gastric functions [55,79]. These results indicate that PYY has a direct action in DVC neurons to stimulate gastric acid secretion. The PYY action is independent from, but may be interactive with, the actions of TRH and 5-HT.

A variety of PYY and NPY derivatives were used to characterize the pharmacological profile of the receptor mediating the acid stimulatory response to PYY microinjected into the DVC [92]. The rat/porcine (r/p) Pro^{34}PYY and human (h) Pro^{34}PYY microinjected into the DVC resulted in a similar dose-related increase in net acid secretion, which was about 33% less potent compared with the acid stimulatory action of PYY [92,95]. Rat/h NPY and pNPY also induced a similar net increase of gastric acid secretion after being microinjected into the DVC, which was about 60% less potent than PYY. Microinjection of PP, r/h[Leu^{31}, Pro^{34}]NPY or the Y2 selective agonists, $hPYY_{3–36}$, $pNPY_{5–36}$ or $pNPY_{13–36}$ at doses ranging from 25 to 168 pmol failed to influence basal gastric acid secretion [92]. The rank order of potency of PYY > r/pPro^{34}PYY = hPro^{34}PYY > r/hNPY = pNPY to stimulate gastric acid secretion upon microinjection into the DVC and the ineffectiveness of PP, [Leu^{31}, Pro^{34}]NPY and C-terminal NPY/PYY fragments suggest that a PYY-preferring, Y1-like receptor subtype is involved in mediating the stimulatory effect of PYY on DVC neurons [92]. This viewpoint was supported by the observation on gastric motility. Chen and Rogers [14] reported that in contrast to the inhibition on TRH-induced gastric motility by DVC microinjected PYY Y2 agonist, a strong stimulation on basal gastric motility was observed after microinjection of PYY Y1 agonist into the DVC.

Chemical stimulation of the DVC, such as injecting exogenous TRH into the DVC [24,40] or increasing endogenous TRH release in the DVC via the stimulation of the raphe nuclei [23,93], induces vagally mediated elevation of gastric secretory and motor functions. However, when the DVC neurons are stimulated with subthreshold doses of these stimuli that do not change acid secretion or motility, gastric protection against ulcerations was observed. It has been established that stimulating DVC-induced gastric protection is mediated by vagal-cholinergic pathways and gastric calcitonin gene-related peptide (CGRP) and L-arginine/nitric oxide (NO)-dependent gastric vasodilation [42,43,45,46,80]. A similar pattern of this dose-related distinction in gastric response was also observed in the central actions of PYY. PYY ic injected at 23 and 47 pmol did not influence gastric acid secretion, however it did reduce gastric lesions induced by ethanol (45%) by 27% and 63% respectively [90]. The gastric protective action of ic injected PYY is independent of medullary TRH, since the action of PYY was not prevented by pretreatment with ic TRH receptor antisense oligodeoxynucleotide [90]. However, the actions of the two peptides are additive. PYY and TRH induced gastric protection when co-injected ic with subthreshold doses that did not show any prevention on the gastric mucosal damage when injected alone [44]. The ic PYY protective action is abolished by CGRP receptor antagonist and by NO synthase inhibitor, indicating the mediation of vagal-cholinergic pathways and the involvement of gastric CGRP and NO releases upon the central vagal stimulation by ic PYY [90]. Similar to the gastric acid stimulatory action of PYY microinjected into the DVC, the gastric protective action of ic injected PYY is also mediated through a PYY preferring, Y1-like receptor. This was shown by the rank order of potency for different PYY and NPY derivatives to protect gastric mucosa against ethanol injury [44], which is similar to that observed for the stimulation of gastric acid secretion by PYY related peptides upon microinjection into the DVC [90,92].

Data showing the protective action of PYY on gastric erosions and the stimulation on acid secretion indicate that,

besides the inhibition of DVC neurons via Y2 receptors, PYY central action includes activation of vagal efferent projections to the stomach through a PYY preferring, Y1-like receptor. Direct extracellular recording of the electric activity of DVC neurons by Chen and Rogers [12] revealed that PYY exerts an excitatory action on about 6–7% of DVC neurons when applied at a low dose (20 fmol). Whether the percentages representing PYY inhibitory and excitatory actions on the DVC neurons change with the PYY dosage or specific PYY receptor subtype agonists applied remains unknown. In addition, the integration of the inhibitory and excitatory actions of PYY in the DMN neurons on the regulation of gastric functions and the physiological significance of this integration are yet to be studied.

4.5. PYY stimulates gastric acid secretion in other medullary vagal related nuclei and the spinal cord

Besides the peripherally originated PYY entering the brain from circulation, PYY immunoreactivity was detected in the brain and the spinal cord with the highest concentration located in the brainstem [9]. A restricted population of neurons in the midline of the rostral medulla expresses PYY mRNA [69]. The raphe pallidus (Rpa) and raphe obscurus (Rob) are medullary nuclei regulating vagal activity through their projections innervating the DVC [41,55,93,94]. The nucleus ambiguus (Amb) is another medullary location of vagal motor neurons projecting to the viscera [53](Fig. 1). PYY nerve terminals are located in the Rpa, Rob and the Amb in addition to the DVC [9], suggesting a possible action of PYY at these nuclei. In urethane-anesthetized rats, PYY microinjected into the Rpa, Rob and the Amb at the dose of 47 pmol/rat significantly increased basal gastric acid secretion, though the effects were 30–70% less potent than the PYY stimulatory action in the DVC [95]. It was reported that pentagastrin-stimulated gastric acid secretion was increased following PYY administration into the thoracic (T8-T10) region of the spinal cord [86]. Whether the stimulatory action of PYY on gastric acid secretion in these medullary nuclei and the spinal cord has any physiological significance will require further study.

5. PYY acts on gastric mucosal ECL cells to inhibit gastric acid secretion

There is convincing evidence suggesting that PYY acts peripherally to inhibit gastric acid secretion. Guo et al. [30] have reported that PYY inhibited pentagastrin-induced gastric acid secretion in dogs after atropine treatment and vagotomy, indicating that the inhibitory action of PYY is in part independent of long and short cholinergic pathways. This view was supported by observations in denervated Heidenhain pouch of dogs [103]. PYY at a dose of 100 pmol/kg/h significantly inhibited gastric acid secretion in the Heidenhain pouch in both interdigestive and postprandial states [103].

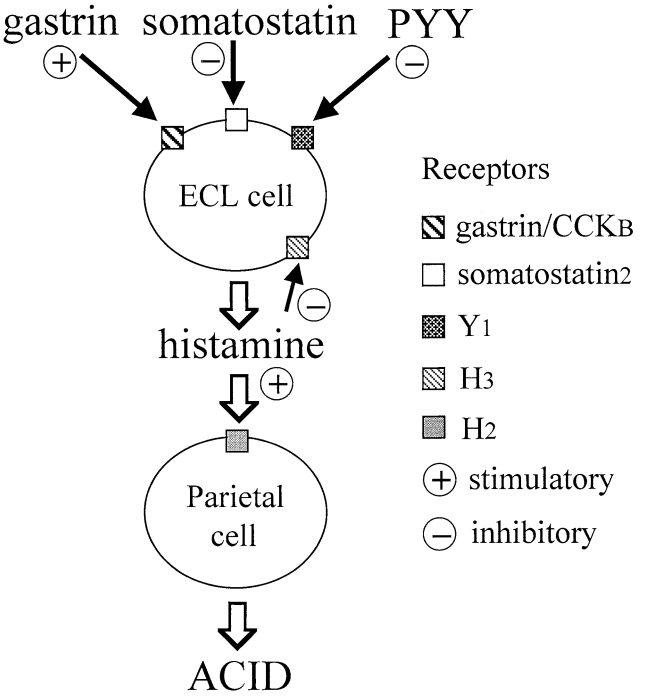

Fig. 3. Simplified relations among gastrin, somatostatin and PYY in their regulation of gastric acid secretion through acting on ECL cells. For detail see References [75,76].

The peripheral regulation of gastric acid secretion from the parietal cells is achieved by interplay between three major gastric endocrine cells: the ECL cell, the gastrin or G cell, and the somatostatin or D cell. The regulation of the functions of these cells is via stimulatory or inhibitory paracrine, endocrine, and neural pathways [75,76]. Histamine released from ECL cells in the gastric corpus plays a critical role in the stimulation of gastric acid secretion from the parietal cells [33,34,70]. Upregulation of ECL cell function is determined by activation of cholecystokinin (CCK)-B receptors, by gastrin, and by activation of β-adrenergic receptors, as well as by acetylcholine in some (10–29%) of the cells. Inhibition of ECL cell histamine release and calcium signaling is produced by somatostatin acting at a type 2 receptor and histamine acting at a histamine-3 receptor [15,33,71,72,76] (Fig. 3).

5.1. PYY peripheral inhibitory action on gastric acid secretion is neither through regulating other gastrointestinal hormones nor a direct action on parietal cells

In dogs, PYY iv infusion at 400 pmol/kg/h, which strongly inhibited the cephalic phase of gastric acid secretion stimulated by iv 2-DG, did not inhibit the release of gastrin and had no significant effect on either the basal release of secretin, gastric inhibitory polypeptide, PP and

neurotensin, or on the release of PP stimulated by 2-DG [32]. The specific binding of gastrin to its receptors on the fundic mucosa was also unaffected by PYY [32]. PYY inhibits gastric acid secretion without influencing plasma gastrin and somatostatin concentrations was confirmed in other studies in dogs and human volunteers [22,88]. In the isolated, vascularly perfused rat stomach, PYY perfused at concentrations of 10 pM to 100 nM did not change either somatostatin or gastrin secretion [19,26]. PYY inhibitory action is also independent of prostaglandin synthesis, as it was not prevented by indomethacin treatment [31]. These results indicate that the PYY inhibitory actions are not mediated by either a negative effect on gastrin release or a positive effect on the release of some established acid inhibitors. The results also do not suggest an inhibition of gastrin binding to its receptors on the fundic cells by PYY.

Whether PYY has a direct inhibitory action on parietal cells has been studied with isolated human and rabbit gastric gland preparation using aminopyrine accumulation as an index of the parietal cell response [48]. PYY, in contrast to somatostatin, was unable to induce any inhibition of the parietal cell response to db-cAMP or histamine in the isolated gastric gland preparation irrespective of the species studied [48].

5.2. PYY regulates ECL cell function through Y1 receptors

Recent interesting findings of Zeng et al. [104,105] revealed that PYY directly inhibits gastric ECL cell functions in rats. Histamine release and changes in intracellular calcium concentration detected by video imaging were analyzed in short-term cultures of isolated rat gastric ECL cells. PYY inhibited gastrin-stimulated histamine release with an ED50 of 2×10^{-9} mol/liter. The calcium entry was also inhibited by PYY. Pro^{34}PYY showed a similar effect as that of PYY while $PYY_{3–36}$ had no effect, indicating that the inhibitions are through Y1 receptors. Using reverse-transcription polymerase chain reaction (RT-PCR) to analyze ECL cell RNA, it was confirmed that the receptor involved was the nontruncated Y1 isoform [105]. Additive but not synergistic inhibitory effects of PYY and somatostatin on gastrin-stimulated ECL cell release of histamine were observed [105]. The inhibitory action of PYY and Pro^{34}PYY on gastrin-stimulated histamine release and calcium signaling was eliminated by pretreatment with pertussis toxin at the dose of 200 ng/mL [105]. Further investigations on the voltage-dependent Ca^{2+} channels (VDCC) of the ECL cells revealed that PYY dose dependently inhibited L-type Ca^{2+} channels, one of the types of VDCC, via a pertussis toxin-sensitive pathway [104]. PYY completely inhibited tetraethylammonium-induced Ca^{2+} oscillations as well as histamine release with a maximal inhibition of 90%. PYY also inhibited high-K^+-induced $[Ca^{2+}]$i increases and histamine release [104]. These studies identified the peripheral cellular target for PYY to inhibit gastric acid secretion. The results indicated that activation of a Y1 inhibitory receptor subtype presenting on the gastric ECL cells to inhibit gastrin-induced ECL cell histamine release and Ca^{2+} entry by interaction with a G(i) or G(o) protein may account for the peripheral inhibitory action of PYY (Fig. 3).

To support the view that PYY regulates the functions of gastric endocrine cells, a recently published study suggests that PYY may exert a direct inhibitory effect on gastric serotonin release from the enterochromaffin (EC) cells in perfused rat stomach. Since the effect was not influenced by tetrodotoxin, the result indicates that the PYY action did not involve the mediation of neural pathways [102].

In vivo studies in awake rabbit with chronic gastric fistula showed that PYY and Pro^{34} PYY inhibited insulin-stimulated gastric acid secretion while $PYY_{3–36}$ did not [51], supporting the above in vitro findings that Y1 receptors are involved in the PYY inhibitory action on gastric acid secretion.

6. PYY may not play a major role in intestinal fat-induced inhibition of gastric acid secretion

Intestinal fat inhibits gastric acid secretion and induces release of PYY into the circulation. Therefore, PYY has been considered as a potent enterogastrone. Recently, Fung et al. [22] reported that the PYY release in response to intraduodenal fat implicates CCK A receptor-dependent pathway. This fat-induced, CCK-mediated stimulation of PYY release from L-cells is accompanied with release of colocalized GLP-1, which is also a potent inhibitor of gastric acid secretion [22]

Among various inhibitory hormones that are released in response to intestinal fat, whether PYY plays a major role in intestinal fat-induced inhibition of gastric secretion and motility has been investigated using immunoneutralization with the PYY polyclonal antibody produced by the Antibody Core at CURE, UCLA. In particular, the role of PYY was compared with that of CCK. In dogs equipped with gastric, duodenal, and midgut fistulas, PYY antibody at the dose of 0.5 mg/kg, or CCK-A receptor antagonist devazepide at the dose of 0.1 mg/kg, was administered 10 min before 60 mM oleate was perfused into the proximal half of the gut. Peptone-induced gastric acid secretion and gastric emptying were inhibited by intestinal fat. The inhibition was reversed by CCK-A receptor antagonist but not by PYY antibody [107]. Similar results were obtained in experiments with rat models. Gastric emptying of liquids was measured by Raybould et al. [73] in awake rats fitted with a Thomas gastric cannula. Intralipid perfused into duodenal or mid-intestinal cannula produced a 46% and 66% inhibition of gastric emptying, which was unaffected by administration of PYY antibody but was abolished by administration of the CCK A receptor antagonist devazepide (0.1 mg/kg ip) [73]. In urethane-anesthetized rats, intraduodenal intralipid (5%, 10% and 20%) administered 20 min before ic

injection of TRH analog dose-dependently reduced by 24%, 83% and 100% respectively the acid response to ic TRH analog. The inhibitory effect of intraduodenal intralipid was completely prevented by CCK A receptor antagonist devazepide but not by iv PYY antibody (Yang et al., unpublished observations). In these studies, the ineffectiveness of PYY antibody was not a result of insufficient doses, since the doses used had been shown to completely prevent exogenous PYY inhibitory actions on gastric emptying and acid secretion [73,91]. In humans, intraduodenal fat significantly inhibited gastrin-stimulated gastric acid secretion by 74%, however PYY iv infusion to produce a PYY blood concentration similar to that obtained after intraduodenal fat failed to induce any change in the acid response to gastrin [38]. These observations indicate that PYY release into the circulation does not play a major role in the inhibition of gastric acid secretion and the delay of gastric emptying induced by intestinal fat. By contrast, the inhibition of gastric functions by intestinal fat is mediated via CCK-dependent mechanisms.

7. Summary and perspectives

Recent studies related to PYY regulation of gastric acid secretion have focused on three aspects, the central action of PYY on medullary vagal regulatory nuclei, the peripheral action of PYY on gastric endocrine cells, and the physiological relevance of circulating PYY in the regulation of postprandial acid secretion. Circulating PYY may enter the brain through the area postrema and portions of the NTS to inhibit through Y2 receptors, and to stimulate through PYY preferring, Y1 like receptors, the activity of cholinergic vagal efferent neurons in the DMN. At the peripheral level, one of the mechanisms for PYY to inhibit gastric acid secretion is to reduce histamine release, which is mediated by Y1 receptors located on the ECL cells

Despite these findings, the exact regulatory roles of PYY in the brain and the stomach on gastric acid secretion are not fully elucidated. So far, most of the data on the PYY action in the brainstem were obtained with pharmacological approaches. The cloned Y1, Y2 and Y4 receptors were recently reported to be located in the AP and DVC using in situ hybridization [67]. However, since this study was targeted on observing the entire central nervous system, the description on Y receptors in medullary vagal regulatory nuclei was less sufficient. More detailed morphologic studies on the distribution of PYY receptors in neurons of the DVC and other brainstem nuclei that are involved in the central regulation of autonomic functions will be important to establish an anatomic background for further studies. To localize specific Y receptors on neurons synthesizing identified neuropeptides or transmitters, or on neurons projecting to form a known neural pathway will be necessary to reveal the mechanism of the PYY action in this area. In addition, experiments should be designed to further study the influence of different PYY doses and receptor ligands on the electrophysiological characteristics of the DVC neurons. Difference in the response to PYY between the DMN and NTS neurons should be investigated. The interactions between PYY and established DVC neuropeptides or neurotransmitters shown to regulate gastric functions, such as TRH, substance P [55,56], 5-HT [98,99], glutamate and GABA [39], should be studied using electrophysiological approaches as recently reported in the study of interactions between TRH and 5-HT in the DVC [10]. These investigations will provide evidence to interpret the integrated PYY inhibitory and stimulatory actions in the DVC on gastric functions.

It is particularly important to note that NPY neurons are widely distributed in the lower brainstem and NPY fibers selectively and densely innervate vagal-regulatory nuclei, such as the DVC, the raphe nuclei and the parapyramidal regions [16,89,our observation]. NPY microinjected into the DVC modulates gastrointestinal [92,97,100] and cardiovascular [96] functions through the vagus. Although PYY was more potent than NPY to stimulate gastric acid secretion when microinjected into the DVC [92], the suggested PYY preferring receptor in this area [44,92] has not been cloned. Since both PYY and NPY act on Y receptors, to distinguish the vagal regulatory actions in the DVC of peripherally originated PYY from those of brain originated NPY, and the physiological significances of these actions still require further studies.

Peripherally, PYY immunoreactivity was detected not only in the lower intestine, but also in neural elements, including the myenteric ganglia, and in endocrine cells in the upper digestive tract of the rat, cat, ferret, pig [8] and dog [58] using antibodies that do not recognize NPY and PP. The presence of PYY in the upper digestive tract was confirmed by radioimmunoassay combined with high-performance liquid chromatography (HPLC) [8,58]. In the stomach, PYY-immunoreactive endocrine cells in the antrum were numerous and constituted a subpopulation of the gastrin-containing cells while in the oxyntic mucosa few were located and found containing somatostatin [8]. The presence of PYY-immunoreactive neuronal and endocrine cell bodies in the stomach indicates that at least some of the PYY actions to inhibit gastric acid secretion may involve local neural or endocrine/paracrine regulation. In the preparation of longitudinal muscle with myenteric plexus of the guinea pig ileum, PYY is more potent than NPY to inhibit transmural stimulation caused contractile motility by depressing the release of acetylcholine from the myenteric plexus [81]. The stimuli that activate the PYY-containing neural and endocrine cells in the stomach, the responsiveness of these PYY cells to intestinal nutrition, and the role of PYY in these cells in the regulation of gastric acid secretion are to be studied. If PYY cells in the stomach do respond to intestinal fat and exert neural or paracrine regulation on inhibiting histamine release from ECL cells, the fat-induced inhibition of gastric acid secretion may not be

prevented by immunoneutralization of circulating PYY. Further studies on the regulation and functions of PYY containing neural and endocrine cells in the stomach may provide valuable information on the peripheral mechanism of PYY regulation of gastric acid secretion and its physiological significance.

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References

[1] Adrian TE, Bacarese-Hamilton AJ, Smith HA, Chohan P, Manolas KJ, Bloom SR. Distribution and postprandial release of porcine peptide YY. J Endocrinol 1987;113:11–14.
[2] Adrian TE, Savage AP, Sagor GR, Allen JM, Bacarese-Hamilton AJ, Tatemoto K, Polak JM, Bloom SR. Effect of peptide YY on gastric, pancreatic, and biliary function in humans. Gastroenterology 1985; 89:494–9.
[3] Ali-Rachedi A, Varndell IM, Adrian TE, Gapp DA, Van NS, Bloom SR, Polak JM. Peptide YY (PYY) immunoreactivity is co-stored with glucagon-related immunoreactants in endocrine cells of the gut, and pancreas. Histochemistry 1984;80:487–91.
[4] Aponte GW, Park K, Hess R, Garcia R, Taylor IL. Meal-induced peptide tyrosine tyrosine inhibition of pancreatic secretion in the rat. FASEB J 1989;3:1949–55.
[5] Bado A, Cloarec D, Moizo L, Laigneau JP, Bataille D, Lewin MJ. Neurotensin and oxyntomodulin-(30–37) potentiate PYY regulation of gastric acid and somatostatin secretions. Am J Physiol 1993;265:G113–7.
[6] Balasubramaniam AA. Neuropeptide Y family of hormones: receptor subtypes, and antagonists. Peptides 1997;18:445–57.
[7] Bonaz B, Taylor I, Taché Y. Peripheral peptide YY induces c-fos-like immunoreactivity in the rat brain. Neurosci Lett 1993;163:77–80.
[8] Bottcher G, Ekblad E, Ekman R, Hakanson R, Sundler F. Peptide YY: a neuropeptide in the gut. Immunocytochemical and immunochemical evidence. Neuroscience 1993;55:281–90.
[9] Hokfelt T, Terenius L. Peptide YY (PYY)-immunoreactive neurons in the lower brain stem, and spinal cord of rat. Acta Physiol Scand 1985;125:349–52.
[10] de TRH uncovers the presence of presynaptic 5-HT1A receptors via activation of a second messenger pathway in the rat dorsal vagal complex. J Physiol 2001;531:425–35.
[11] Chen CH, Rogers RC. Central inhibitory action of peptide YY on gastric motility in rats. Am J Physiol 1995;269:R787–92.
[12] YY, and the Y2 agonist PYY-(13–36) inhibit neurons of the dorsal motor nucleus of the vagus. Am J Physiol 1997;273:R213–8.
[13] Chen CH, Rogers RC, Stephens RLJ. Intracisternal injection of peptide YY inhibits gastric emptying in rats. Regul Pept 1996;61:95–8.
[14] Chen CH, Stephens RLJ, Rogers RC. PYY, and NPY: control of gastric motility via action on Y1, and Y2 receptors in the DVC. Neurogastroenterol Motil 1997;9:109–16.
[15] Chen D, Zhao CM, Lindstrom E, Hakanson R. Rat stomach ECL cells up-date of biology and physiology. Gen Pharmacol 1999;32:413–22.
[16] Chronwall BM, DiMaggio DA, Massari VJ, Pickel VM, Ruggiero DA, O'Donohue TL. The anatomy of neuropeptide-Y-containing neurons in rat brain. Neuroscience 1985;15:1159–81.
[17] Clave P, Lluis F, Thompson JC, Greeley GHJ. Peptide YY inhibits gastric acid secretion stimulated by the autonomic nervous system. Biol Signals 1992;1:40–5.
[18] Dumont Y, Fournier A, St-Pierre S, Quirion R. Autoradiographic distribution of [125I]Leu31,Pro34]PYY and [125I]PYY3–36 binding sites in the rat brain evaluated with two newly developed Y1 and Y2 receptor radioligands. Synapse 1996;22:139–58.
[19] Eissele R, Koop H, Arnold R. Effect of peptide YY on gastric acid secretion, gastrin and somatostatin release in the rat. Z Gastroenterol 1990;28:129–31.
[20] el-Salhy M, Wilander E, Juntti-Berggren L, Grimelius L. The distribution and ontogeny of polypeptide YY (PYY)- and pancreatic polypeptide (PP)-immunoreactive cells in the gastrointestinal tract of rat. Histochemistry 1983;78:53–60.
[21] Fenstermacher J, Gross P, Sposito N, Acuff V, Pettersen S, Gruber K. Structural and functional variations in capillary systems within the brain. Ann N Y Acad Sci 1988;529:21–30.
[22] Fung LC, Chisholm C, Greenberg GR. Glucagon-like peptide-1-(7–36) amide, and peptide YY mediate intraduodenal fat-induced inhibition of acid secretion in dogs. Endocrinology 1998;139:189–94.
[23] Garrick T, Prince M, Yang H, Ohning G, Taché Y. Raphe pallidus stimulation increases gastric contractility via TRH projections to the dorsal vagal complex in rats. Brain Res 1994;636:343–7.
[24] Garrick T, Stephens R, Ishikawa T, Sierra A, Avidan A, Weiner H, Taché Y. Medullary sites for TRH analogue stimulation of gastric contractility in the rat. Am J Physiol 1989;256:G1011–5.
[25] Grandt D, Schimiczek M, Beglinger C, Layer P, Goebell H, Eysselein VE, Reeve JRJ. Two molecular forms of peptide YY (PYY) are abundant in human blood: characterization of a radioimmunoassay recognizing PYY 1–36 and PYY 3–36. Regul Pept 1994;51:151–9.
[26] Greeley GHJ, Guo YS, Gomez G, Lluis F, Singh P, Thompson JC. Inhibition of gastric acid secretion by peptide YY is independent of gastric somatostatin release in the rat. Proc Soc Exp Biol Med 1988; 189:325–8.
[27] Greeley GHJ, Hashimoto T, Izukura M, Gomez G, Jeng J, Hill FL, Lluis F, Thompson JC. A comparison of intraduodenally, and intracolonically administered nutrients on the release of peptide-YY in the dog. Endocrinology 1989;125:1761–5.
[28] Greeley GHJ, Jeng YJ, Gomez G, Hashimoto T, Hill FL, Kern K, Kurosky T, Chuo HF, Thompson JC. Evidence for regulation of peptide-YY release by the proximal gut. Endocrinology 1989;124: 1438–43.
[29] Gross PM, Wall KM, Pang JJ, Shaver SW, Wainman DS. Microvascular specializations promoting rapid interstitial solute dispersion in nucleus tractus solitarius. Am J Physiol 1990;259:R1131–8.
[30] Guo YS, Fujimura M, Lluis F, Tsong Y, Greeley GH, Thompson JC. Inhibitory action of peptide YY on gastric acid secretion. Am J Physiol 1987;253:G298–302.
[31] Guo YS, Fujimura M, Lluis F, Tsong Y, Greeley GHJ, Thompson JC. Inhibitory action of peptide YY on gastric acid secretion. Am J Physiol 1987;253:G298–302.
[32] Guo YS, Singh P, Gomez G, Greeley GHJ, Thompson JC. Effect of peptide YY on cephalic, gastric, and intestinal phases of gastric acid secretion and on the release of gastrointestinal hormones. Gastroenterology 1987;92:1202–8.
[33] Hakanson R, Chen D, Andersson K, Monstein HJ, Zhao CM, Ryberg B, Sundler F, Mattsson H. The biology and physiology of the ECL cell. Yale J Biol Med 1994;67:123–34.
[34] Hakanson R, Chen D, Tielemans Y, Andersson K, Ryberg B, Sundler F, Mattsson H. ECL cells: biology, and pathobiology. Digestion. 1994;55(Suppl 3):38–45.
[35] Hashimoto Y, Nagahata Y, Urakawa T, Saitoh Y. [Inhibitory effect of peptide YY on gastric acid output in rats]. Nippon Shokakibyo Gakkai Zasshi 1992;89:1–8.
[36] Hashimoto Y, Sano I, Nagahata Y, Wang ZT, Itoh A, Takeda K, Ichihara T, Moritomo H, Urakawa T, Saitoh Y. Inhibitory effect of peptide YY on gastric acid output in rats. Scand J Gastroenterol Suppl 1989;162:134–7.

[37] Hernandez EJ, Whitcomb DC, Vigna SR, Taylor IL. Saturable binding of circulating peptide YY in the dorsal vagal complex of rats. Am J Physiol 1994;266:G511–6.
[38] Hoentjen F, Hopman WP, Maas MI, Jansen JB. Role of circulating peptide YY in the inhibition of gastric acid secretion by dietary fat in humans. Scand J Gastroenterol 2000;35:166–71.
[39] Hornby PJ. Receptors and transmission in the brain-gut axis II. Excitatory amino acid receptors in the brain-gut axis. Am J Physiol Gastrointest Liver Physiol 2001;280:G1055–60.
[40] Ishikawa T, Yang H, Taché Y. Medullary sites of action of the TRH analogue, RX 77368, for stimulation of gastric acid secretion in the rat. Gastroenterology 1988;95:1470–6.
[41] Kaneko H, Taché Y. TRH in the dorsal motor nucleus of vagus is involved in gastric erosion induced by excitation of raphe pallidus in rats. Brain Res 1995;699:97–102.
[42] Kaneko H, Yang H, Ohning G, Taché Y. Medullary TRH is involved in gastric protection induced by low dose of kainic acid into the raphe pallidus. Am J Physiol.; 1995;268:G548–52.
[43] Kato K, Yang H, Taché Y. Low doses of TRH analogue act in the dorsal motor nucleus to induce gastric protection in rats. Am J Physiol 1995;269:R1301–7.
[44] Kawakubo K, Yang H, Taché Y. Intracisternal PYY inhibits gastric lesions induced by ethanol in rats: role of PYY-preferring receptors? Brain Res 2000;854:30–4.
[45] Kiraly A, Suto G, Guth PH, Tache Y. Mechanisms mediating gastric hyperemic and acid responses to central TRH analog at a cytoprotective dose. Am J Physiol 1997;273:G31–8.
[46] Kiraly A, Suto G, Tache Y. Role of nitric oxide in the gastric cytoprotection induced by central vagal stimulation. Eur J Pharmacol 1993;240:299–301.
[47] Leduque P, Paulin C, Dubois PM. Immunocytochemical evidence for a substance related to the bovine pancreatic polypeptide-peptide YY group of peptides in the human fetal gastrointestinal tract. Regul Pept 1983;6:219–30.
[48] Leth R, Lundell L, Olbe L. Effects of some gastrointestinal peptides on isolated human and rabbit gastric glands. Scand J Gastroenterol 1991;26:89–96.
[49] Li Y, Hao Y, Zhu J, Owyang C. Serotonin released from intestinal enterochromaffin cells mediates luminal non-cholecystokinin-stimulated pancreatic secretion in rats. Gastroenterology 2000;118:1197–207.
[50] Lloyd KC, Amirmoazzami S, Friedik F, Heynio A, Solomon TE, Walsh JH. Candidate canine enterogastrones: acid inhibition before and after vagotomy. Am J Physiol 1997;272:G1236–42.
[51] Lloyd KC, Grandt D, Aurang K, Eysselein VE, Schimiczek M, Reeve JRJ. Inhibitory effect of PYY on vagally stimulated acid secretion is mediated predominantly by Y1 receptors. Am J Physiol 1996;270: G123–7.
[52] Lluis F, Gomez G, Fujimura M, Greeley GHJ, Townsend CMJ, Thompson JC. Peptide YY interacts with secretin, and duodenal acidification to inhibit gastric acid secretion. Regul Pept 1987;18: 155–63.
[53] Loewy AD, Spyer KM. Vagal preganglionic neurons. In: Loewy AD, Spyer KM, editors. Central regulation of autonomic function. London: Oxford University Press, 1990. p. 68–87.
[54] Lynch DR, Walker MW, Miller RJ, Snyder SH. Neuropeptide Y receptor binding sites in rat brain: differential autoradiographic localizations with 125I-peptide YY, and 125I- neuropeptide Y imply receptor heterogeneity. J Neurosci 1989;9:2607–19.
[55] Lynn RB, Kreider MS, Miselis RR. Thyrotropin-releasing hormone-immunoreactive projections to the dorsal motor nucleus, and the nucleus of the solitary tract of the rat. J Comp Neurol 1991;311:271–88.
[56] Manaker S, Rizio G. Autoradiographic localization of thyrotropin-releasing hormone and substance P receptors in the rat dorsal vagal complex. J Comp Neurol 1989;290:516–26.
[57] McCann MJ, Rogers RC. Functional and Chemical Anatomy of a Gastric Vago-Vagal Reflex. In: Taché Y, Wingate D, Burks TF, editors. Innervation of the Gut: Pathophysiological Implications. London: CRC Press, 1993. p. 81–92.
[58] McDonald TJ, Wang YF, Mao YK, Broad RM, Cook MA, Daniel EE. PYY: a neuropeptide in the canine enteric nervous system. Regul Pept 1993;44:33–48.
[59] Morgan JI, Curran T. Stimulus-transcription coupling in neurons: role of cellular immediate- early genes. Trends Neurosci 1989;12:459–62.
[60] O-Lee TJ, Wei JY, Taché Y. Intracisternal TRH, and RX 77368 potently activate gastric vagal efferent discharge in rats. Peptides 1997;18:213–9.
[61] Olsen O, Christiansen J. Inhibition of human gastric acid secretion by peptide YY and secretin. Digestion 1990;47:156–9.
[62] Pappas TN, Debas HT, Chang AM, Taylor IL. Peptide YY release by fatty acids is sufficient to inhibit gastric emptying in dogs. Gastroenterology 1986;91:1386–9.
[63] Pappas TN, Debas HT, Goto Y, Taylor IL. Peptide YY inhibits meal-stimulated pancreatic, and gastric secretion. Am J Physiol 1985; 248:G118–23.
[64] Pappas TN, Debas HT, Goto Y, Taylor IL. Peptide YY inhibits meal-stimulated pancreatic, and gastric secretion. Am J Physiol 1985; 248:G118–23.
[65] Pappas TN, Debas HT, Taylor IL. Enterogastrone-like effect of peptide YY is vagally mediated in the dog. J Clin Invest 1986;77:49–53.
[66] Pardridge WM. Neuropeptides and the blood-brain barrier. Annu Rev Physiol 1983;45:73–82.
[67] Parker RM, Herzog H. Regional distribution of Y-receptor subtype mRNAs in rat brain. Eur J Neurosci 1999;11:1431–48.
[68] Paxinos G, Watson, C. *The Rat Brain in Stereotaxic Coordinates*, 3rd ed. San Diego: Academic Press. 1997. p. 1–79.
[69] Pieribone VA, Brodin L, Friberg K, Dahlstrand J, Soderberg C, Larhammar D, Hokfelt T. Differential expression of mRNAs for neuropeptide Y-related peptides in rat nervous tissues: possible evolutionary conservation. J Neurosci 1992;12:3361–71.
[70] Prinz C, Kajimura M, Scott DR, Mercier F, Helander HF, Sachs G. Histamine secretion from rat enterochromaffinlike cells. Gastroenterology 1993;105:449–61.
[71] Prinz C, Sachs G, Walsh JH, Coy DH, Wu SV. The somatostatin receptor subtype on rat enterochromaffinlike cells. Gastroenterology 1994;107:1067–74.
[72] Prinz C, Zanner R, Gerhard M, Mahr S, Neumayer N, Hohne-Zell B, Gratzl M. The mechanism of histamine secretion from gastric enterochromaffin-like cells. Am J Physiol 1999;277:C845–55.
[73] Raybould HE, Tabrizi Y, Meyer JH, Walsh JH. PYY immunoneutralization does not alter lipid-induced inhibition of gastric emptying in rats. Regul Pept 1999;79:125–30.
[74] Rudnicki M, Rigel DF, McFadden DW. Vagal cooling blocks circulating neuropeptide Y (NPY), peptide YY (PYY), and pancreatic polypeptide (PP) release. J Surg Res 1991;51:40–5.
[75] Sachs G, Prinz C, Loo D, Bamberg K, Besancon M, Shin JM. Gastric acid secretion: activation and inhibition. Yale J Biol Med 1994;67: 81–95.
[76] Sachs G, Zeng N, Prinz C. Physiology of isolated gastric endocrine cells. Annu Rev Physiol 1997;59:243–56.
[77] Sheikh SP, Holst JJ, Orskov C, Ekman R, Schwartz TW. Release of PYY from pig intestinal mucosa; luminal and neural regulation. Regul Pept 1989;26:253–66.
[78] Stephens RL, Ishikawa T, Weiner H, Novin D, Taché Y. TRH analogue, RX 77368, injected into dorsal vagal complex stimulates gastric secretion in rats. Am J Physiol 1988;254:G639–43.
[79] Taché Y, Yang H. Role of medullary TRH in the vagal regulation of gastric function. In: Wingate DL, Butkd TF, editors. Innervation of the Gut: Pathophysiological Implications. Boca Raton: CRC, 1994. p. 67–80.

[80] Taché Y, Yoneda M. Central action of TRH to induce vagally mediated gastric cytoprotection and ulcer formation in rats. J Clin Gastroenterol 1993;17(Suppl 1):S58–63.
[81] Takahashi T, Yamamura T, Utsunomiya J. Human pancreatic polypeptide, neuropeptide Y and peptide YY reduce the contractile motility by depressing the release of acetylcholine from the myenteric plexus of the guinea pig ileum. Gastroenterol Jpn 1992;27:327–33.
[82] Tatemoto K. Isolation and characterization of peptide YY (PYY), a candidate gut hormone that inhibits pancreatic exocrine secretion. Proc Natl Acad Sci U S A 1982;79:2514–8.
[83] Taylor IL. Distribution and release of peptide YY in dog measured by specific radioimmunoassay. Gastroenterology 1985;88:731–7.
[84] Taylor IL. Pancreatic polypeptide family: pancreatic polypeptide, neuropeptide Y, and peptide YY. In: Am.Physiol.Soc., editors. Handbook of Physiology. The Gastrointestinal System. Neural and Endocrine Biology. Bethesda, MD: 1989:475–544.
[85] Tougas G, Wang L. Pseudoaffective cardioautonomic responses to gastric distension in rats. Am J Physiol 1999;277:R272–8.
[86] Wager-Page SA, Rosenbaum G, Veale WL, Davison JS. Spinal and peripheral modulation of gastric acid secretion and arterial pressure by neuropeptide Y, peptide YY, and pancreatic polypeptide in rats. Peptides 1993;14:1299–1308.
[87] Wettergren A, Maina P, Boesby S, Holst JJ. Glucagon-like peptide-1 7–36 amide, and peptide YY have additive inhibitory effect on gastric acid secretion in man. Scand J Gastroenterol 1997;32:552–5.
[88] Wettergren A, Petersen H, Orskov C, Christiansen J, Sheikh SP, Holst JJ. Glucagon-like peptide-1 7–36 amide, and peptide YY from the L-cell of the ileal mucosa are potent inhibitors of vagally induced gastric acid secretion in man. Scand J Gastroenterol 1994;29:501–5.
[89] Yamazoe M, Shiosaka S, Emson PC, Tohyama M. Distribution of neuropeptide Y in the lower brainstem: an immunohistochemical analysis. Brain Res 1985;335:109–20.
[90] Yang H, Kawakubo K, Taché Y. Intracisternal PYY increases gastric mucosal resistance: role of cholinergic, CGRP, and NO pathways. Am J Physiol 1999;277:G555–62.
[91] Yang H, Kawakubo K, Wong H, Ohning G, Walsh J, Tache Y. Peripheral PYY inhibits intracisternal TRH-induced gastric acid secretion by acting in the brain. Am J Physiol Gastrointest Liver Physiol 2000;279:G575–81.
[92] Yang H, Li WP, Reeve JRJ, Rivier J, Taché Y. PYY-preferring receptor in the dorsal vagal complex, and its involvement in PYY stimulation of gastric acid secretion in rats. Br J Pharmacol 1998; 123:1549–54.
[93] Yang H, Ohning GV, Taché Y. TRH in dorsal vagal complex mediates acid response to excitation of raphe pallidus neurons in rats. Am J Physiol 1993;265:G880–6.
[94] Yang H, Taché Y. Caudal medullary raphe nuclei and vagal regulation of gastric function. In: Singer MV, Ziegler R, Fohr G, editors. Gastrointestinal Tract and Endocrine System. London: Kluwer Academic Publishers, 1995. p. 39–49.
[95] Yang H, Taché Y. PYY in brain stem nuclei induces vagal stimulation of gastric acid secretion in rats. Am J Physiol 1995;268:G943–8.
[96] Yang SN, Narvaez JA, Bjelke B, Agnati LF, Fuxe K. Microinjections of subpicomolar amounts of NPY(13–36) into the nucleus tractus solitarius of the rat counteract the vasodepressor responses of NPY(1–36) and of a NPY Y1 receptor agonist. Brain Res 1993;621: 126–32.
[97] Yoneda M, Nakamura K, Yokohama S, Tamori K, Sato Y, Aso K, Aoshima M, Kono T, Makino I. Neuropeptide Y stimulates bile secretion via Y1 receptor in the left dorsal vagal complex in rats. Hepatology 1998;28:670–6.
[98] Yoneda M, Taché Y. Potentiating interactions between medullary serotonin and thyrotropin- releasing hormone-induced gastric erosions in rats. Neurosci Lett 1993;161:199–202.
[99] Yoneda M, Taché Y. Serotonin enhances gastric acid response to TRH analogue in dorsal vagal complex through 5-HT2 receptors in rats. Am J Physiol 1995;269:R1–6.
[100] Yoneda M, Yokohama S, Tamori K, Sato Y, Nakamura K, Makino I. Neuropeptide Y in the dorsal vagal complex stimulates bicarbonate- dependent bile secretion in rats. Gastroenterology 1997;112: 1673–80.
[101] You CH, Chey WY. Secretin is an enterogastrone in humans. Dig Dis Sci 1987;32:466–71.
[102] Yu PL, Fujimura M, Hayashi N, Nakamura T, Fujimiya M. Mechanisms in regulating the release of serotonin from the perfused rat stomach. Am J Physiol Gastrointest Liver Physiol 2001;280: G1099–105.
[103] Zai H, Haga N, Fujino MA, Itoh Z. Effect of peptide YY on gastric motor and secretory activity in vagally innervated and denervated corpus pouch dogs. Regul Pept 1996;61:181–8.
[104] Zeng N, Athmann C, Kang T, Walsh JH, Sachs G. Role of neuropeptide-sensitive L-type Ca(2+) channels in histamine release in gastric enterochromaffin-like cells. Am J Physiol 1999;277:G1268–80.
[105] Zeng N, Walsh JH, Kang T, Wu SV, Sachs G. Peptide YY inhibition of rat gastric enterochromaffin-like cell function. Gastroenterology.; 1997;112:127–135.
[106] Zhang T, Brubaker PL, Thompson JC, Greeley GH. Characterization of peptide-YY release in response to intracolonic infusion of amino acids. Endocrinology 1993;132:553–7.
[107] Zhao XT, Walsh JH, Wong H, Wang L, Lin HC. Intestinal fat-induced inhibition of meal-stimulated gastric acid secretion depends on CCK but not peptide YY. Am J Physiol 1999;276:G550–5.