Gastric protective effect of peripheral PYY through PYY preferring receptors in anesthetized rats

KEISHI KAWAKUBO, HONG YANG, AND YVETTE TACHE´

CURE: Digestive Diseases Research Center, Veteran’s Affairs Greater Los Angeles Healthcare System, Department of Medicine, Division of Digestive Diseases and Brain Research Institute, University of California Los Angeles, Los Angeles, California 90073

Received 26 April 2002; accepted in final form 25 July 2002

Kawakubo, Keishi, Hong Yang, and Yvette Tache´. Gastric protective effect of peripheral PYY through PYY preferring receptors in anesthetized rats. Am J Physiol Gastrointest Liver Physiol 283: G1035–G1041, 2002.—The influence of intravenous peptide YY (PYY) on the gastric injury induced by 45% ethanol was investigated in urethane-anesthetized rats. PYY (25, 75, 125, and 250 pmol·kg⁻¹·h⁻¹) significantly reduced gastric lesions by 36, 59, 40, and 38%, respectively. Antibody against rat PYY (2 mg/rat) injected intravenously completely prevented the gastroprotective effect of intravenous PYY (75 pmol·kg⁻¹·h⁻¹), whereas injected intracisternally (460 µg/20 µl) it significantly prevented intracisternal PYY (24 pmol/rat)-induced 58% reduction of ethanol lesions but not that induced by intravenous PYY. Vagotomy did not influence the gastroprotective effect of intravenous PYY. The Y₁/“PYY-preferring” receptor agonist [Pro⁴⁴]PYY (75 pmol·kg⁻¹·h⁻¹ iv) significantly decreased ethanol-induced gastric lesions by 82%, whereas [Leu³¹, Pro⁴⁴]NPY, a Y₁/Y₃ agonist, and PYY-(3–36), a Y₂ agonist, had no effect. These data indicate that PYY-infused intravenously at doses reported to mimic postprandial peak blood levels prevents ethanol-induced gastric injury through vagal independent pathways and PYY-preferring receptors.

neuropeptide Y-receptor subtype; peptide YY antibody; vagotomy; ethanol; gastric lesions

PEPTIDE YY (PYY), neuropeptide Y (NPY), and pancreatic peptide (PP) belong to a family of structurally related 36-amino acid peptides. PYY, which was isolated from porcine duodenum (35), is widely distributed in the gastrointestinal tract, predominantly in the endocrine cells of intestine and pancreas (24, 26) and in neuronal elements of the gastrointestinal tract (7).

Postprandial release of PYY into the circulation has been established in all species studied so far (36). Doses of PYY infused intravenously, reproducing the circulating postprandial peak levels, are in the range of 50–120 pmol·kg⁻¹·h⁻¹ in rats (19, 34). Intravenous infusion of PYY at doses within this range inhibits stimulated gastric acid secretion (1, 16, 28, 30) and gastric emptying (3, 29) in humans and dogs and exocrine pancreatic secretion in rats and dogs (19, 31, 37) and interrupts intestinal propagation in rats (2). PYY is assumed to act as a physiological inhibitor of upper gastrointestinal functions when nutrients reach the distal small intestine (36).

PYY is a gut peptide that also acts in the brain to alter gastric secretory and motor functions through vagal pathways. Autoradiographic studies have demonstrated dense concentrations of PYY binding sites in the rat dorsal medulla (25). Saturable PYY binding has been observed in the region of the brain stem containing the dorsal vagal complex (DVC) after the intravenous injection of ¹²⁵I-labeled PYY at doses reproducing postprandial blood concentrations in rats (18). We previously reported that intravenous PYY-induced inhibition of gastric acid secretion was prevented by intracisternal injection of PYY antibody, providing evidence for a central action of peripheral PYY (42). In addition, microinjection of PYY or NPY into the DVC at low doses inhibits vagally stimulated gastric contractions, whereas higher doses induce a vagal-dependent stimulation of gastric acid and hepatic bile secretion as well as gastric motor function in urethane-anesthetized rats (8, 40, 43–45). Our recent work also revealed that PYY injected intracisternally confers gastric protection against intragastric ethanol-induced gastric mucosal injury through vagal cholinergic-dependent pathways recruiting peripheral CGRP and nitric oxide (NO) mechanisms (20, 41). However, whether circulating PYY exerts a gastroprotective action is still unknown.

It is widely accepted that NPY/PYY/PP binds to and activates at least six Y-receptor subtypes, the cloned Y₁–Y₅ receptors and a “PYY-preferring” receptor, which is yet to be cloned (5). Pharmacological characterization of Y receptors established that [Pro³⁴]PYY has preferential affinity for PYY-preferring/Y₁ receptors, PYY-(3–36) for Y₂, and [Leu³¹, Pro⁴⁴]NPY for Y₁/Y₃/Y₅-receptor subtypes (5). Studies using these prototypic peptide NPY-receptor agonists indicate that the central stimulatory effect of PYY on gastric motility and acid secretion and the central gastroprotective effect are mediated through the activation of Y₁/PYY-

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
preferring receptor (8, 20, 43). On the other hand, PYY injected intracisternally or microinjected into the DVC at low doses induced inhibition of vagally stimulated gastric secretion and motility involves Y2 receptors (8, 42). The inhibition of vagally stimulated gastric acid secretion by intravenous PYY infusion appears also to be mediated by central Y2 receptor (42).

In the present study, we examined whether rat (r/) porcine (p) PYY infused intravenously modulates gastric mucosal injury induced by intragastric ethanol in urethane-anesthetized rats. To gain insight into the PYY site of action, the influence of antibody to r/pPYY (anti-PYY) injected peripherally or centrally on the gastroprotective action of intravenous PYY was investigated as well as the effect of vagotomy. Lastly, the Y-receptor subtype involved in the intravenous PYY-induced reduction of gastric injury to ethanol was assessed using prototypic PYY/NPY agonists with differential affinity for Y-receptor subtypes, namely [Pro34]PYY (PYY-preferring agonist/Y1), PYY-(3–36) (Y2 > PYY preferring), and [Leu31, Pro34]NPY (Y1/Y2/Y3) (5, 15, 23).

MATERIALS AND METHODS

Animals

Animal care and experimental protocols were in accordance with approved protocols of the Veteran Administration Medical Center/West Los Angeles Research Service Animal Committee. Male Sprague-Dawley rats (Harlan Laboratory, San Diego, CA) weighing 250–320 g were maintained under conditions of controlled temperature (22–24°C) and illumination (12:12-h light-dark cycle starting at 6 AM) with ad libitum Purina Laboratory Chow (Ralston Purina, St. Louis, MO) and tap water. Animals were deprived of food for 16 h but had free access to water until 2 h before the beginning of the study. All experiments were performed in rats anesthetized with intraperitoneal injection of urethane (1.25 g/kg, Sigma, St. Louis, MO). The body temperature of rats was maintained at 37°C during the study with electrically heated pad.

Substances and Treatments

r/pPYY, p[Leu31, Pro34] NPY (kindly provided by Dr. J. Rivier, Clayton Foundation Laboratories for Peptide Biology, The Salk Institute, La Jolla, CA), and r/p [Pro34]PYY and r/pPYY-(3–36) (Peptides Synthesis Core Facility, CURE, Digestive Diseases Research Center, UCLA, Los Angeles, CA) were dissolved in 0.1% BSA (Sigma), saline solution before intravenous infusion (1 ml/h) through the right femoral vein. For intracisternal injection, r/pPYY was dissolved in saline.

The PYY antibody #9153 (CURE) was raised against the full-length r/pPYY as previously described (22). The PYY antibody evaluated by radioimmunoassay has an ID50 of 30 fmol/ml for r/pPYY and 120 fmol/ml for r/pPYY-(3–36) and no cross-reactivity with rat or human PP or NPY (ID50 > 10,000 fmol/ml) as previously reported (6, 22). The PYY antibody was purified using protein A-Sepharose column. Normal rabbit (NR) IgG and anti-PYY IgG used for intracisternal injection were concentrated using an S-43–70 Spectra/Por stirred cell with 100 K molecular weight cutoff type C ultrafiltration membranes (Spectrum Medical Industries, Los Angeles, CA) and dialyzed against 20 mM phosphate and 110 mM NaCl (pH 7.0). Concentrations of the IgG proteins were estimated by measuring the optical density of the solution at λ = 280.

For intracisternal injection, the head of the anesthetized rat was fixed with ear bars of stereotaxic equipment and the occipital membrane was punctured using a 50-µl Hamilton syringe (Hamilton, Reno, NV). The correctness of needle placement into the cisterna magna was insured by the presence of cerebrospinal fluid in the Hamilton syringe on aspiration before injection. The intracisternal injection of peptides and related vehicle was performed in 5 µl, and that of PYY antibody and NRlgG was performed in 20 µl.

Gastric Lesion Formation and Assessment

Gastric lesions were induced by intragastric administration of 45% ethanol (5 ml/kg, diluted in saline) using oral intubation with a stainless steel cannula in urethane-anesthetized rats. One hour after ethanol administration, rats were euthanized by CO2 inhalation and the stomachs were removed. The areas of gastric mucosal lesions were measured by a computerized image-analyzer device using the National Institutes of Health image program. Lesions are expressed as percent coverage of the glandular stomach as in our previous studies (20, 41).

Experimental Protocols

Effect of intravenous PYY on ethanol-induced gastric lesions. Intravenous infusion of PYY (25, 75, 125, or 250 pmol·kg⁻¹·h⁻¹) or vehicle (0.1% BSA/saline) was started 30 min before and ended 60 min after the intragastric administration of 45% ethanol (5 ml/kg). Then rats were euthanized, and the stomachs were removed for the measurement of gastric lesions. The regimen of PYY administration was based on a previous dose-response study in fasted, urethane-anesthetized rats showing that PYY infusion in doses ranging from 24 to 240 pmol·kg⁻¹·h⁻¹ increased dose dependently plasma PYY and that postprandial levels are reached 30 min after the infusion of ~120 pmol·kg⁻¹·h⁻¹ (34).

Effect of intravenous anti-PYY on intravenous or intracisternal PYY-induced gastric protection against ethanol. PYY antibody or NRlgG was injected intravenously (2 mg/rat) 10 min before the start of intravenous PYY (75 pmol·kg⁻¹·h⁻¹) or vehicle (0.1% BSA/saline) infusion (1 ml/h) or intracisternal PYY (24 pmol/rat) or saline injection (5 µl). Ethanol (45%, 5 ml/kg) was administered intragastrically 30 min after the start of intravenous PYY infusion or intracisternal PYY injection. Rats were euthanized 60 min later to monitor gastric lesions. The dose of PYY antibody was adjusted based on our previous studies showing that intravenous infusion of PYY at 1 nmol·kg⁻¹·h⁻¹-induced inhibition of the acid response to vagal stimulation was prevented by the intravenous injection of PYY antibody at 4.5 mg/rat (42).

Effect of intracisternal anti-PYY on intravenous or intracisternal PYY-induced gastric protection against ethanol. Anti-PYY or NRlgG (460 µg/rat) was injected intracisternally in 20 µl 10 min before the intravenous infusion of PYY (75 pmol·kg⁻¹·h⁻¹) or vehicle (0.1% BSA/saline) or the intracisternal injection of PYY (24 pmol/rat) or saline. Ethanol (45%, 5 ml/kg) was administered intragastrically 30 min after the start of intravenous PYY infusion or intracisternal PYY injection. Rats were euthanized 60 min later to monitor gastric lesions. The amount of PYY antibody injected intracisternally corresponds to the maximal concentration that could be achieved in 20 µl.

Effect of vagotomy on intravenous PYY-induced gastric protection against ethanol. Bilateral cervical vagotomy or sham operation was performed in urethane-anesthetized rats 2 h before the intravenous infusion of PYY (75 pmol·kg⁻¹·h⁻¹) or vehicle (1% BSA/saline). Ethanol (45%, 5 ml/kg)
was administered intragastrically 30 min after the start of PYY infusion, and rats were euthanized 60 min later to monitor gastric lesions.

**Effects of intravenous NPY/PYY analogs on ethanol-induced gastric lesions.** r/p[Pro34]PYY, p[Leu18, Pro39]NPY, r/pPYY-(3–36) (75 pmol·kg⁻¹·h⁻¹), or vehicle (0.1% BSA/saline) was infused intravenously from 30 min before to 60 min after intragastric administration of ethanol (45%, 5 ml/kg). Rats were euthanized 60 min later, and the gastric lesions were monitored.

**Statistical analysis.** All results are expressed as means ± SE. Multiple-group comparisons were performed by ANOVA followed by Fisher’s protected least-significant differences. A P value <0.05 was considered statistically significant.

**RESULTS**

**Effect of intravenous PYY on ethanol-induced gastric lesions.** Intragastric administration of 45% ethanol by oral intubation (5 ml/kg) produced macroscopic gastric lesions within 60 min visualized as long dark-red vertical lines covering 18.8 ± 2.6% of the corpus mucosa in urethane-anesthetized rats infused intravenously with vehicle. PYY infused intravenously at 25 and 75 pmol·kg⁻¹·h⁻¹ from 30 min before to 60 min after the ethanol administration dose dependently decreased 45% ethanol-induced gastric lesions to 12.0 ± 3.6 (P < 0.05) and 7.8 ± 2.2% (P < 0.05), respectively. PYY infused intravenously at 125 and 250 pmol·kg⁻¹·h⁻¹ reduced significantly gastric erosions induced by ethanol by a similar magnitude as 25 pmol·kg⁻¹·h⁻¹ (11.3 ± 1.4 and 11.7 ± 1.3%, respectively, P < 0.05; Fig. 1). In further studies, PYY was infused at 75 pmol·kg⁻¹·h⁻¹, which results in the maximal protective effect.

**Effect of intravenous anti-PYY on intravenous or intracisternal PYY-induced gastric protection against ethanol.** Anti-PYY injected intravenously (2 mg/rat) did not significantly alter the formation of gastric lesions induced by 45% ethanol in rats infused intravenously or injected intracisternally with respective vehicles (15.1 ± 2.0 and 19.7 ± 2.3%, respectively). PYY infused intravenously (75 pmol·kg⁻¹·h⁻¹) or injected intracisternally (24 pmol/rat) significantly reduced gastric lesions to 5.2 ± 0.8 and 7.0 ± 0.6%, respectively, in rats injected intravenously with NRIgG (2 mg/rat). PYY antibody injected intravenously (2 mg/rat) abolished the gastroprotective effect of intravenous PYY (16.7 ± 3.4%, P < 0.05 vs. intravenous NRIgG) but did not influence the reduction of gastric lesions induced by intracisternal PYY (6.5 ± 1.1%; Fig. 2).

**Effect of intracisternal anti-PYY on intravenous or intracisternal PYY-induced gastric protection against ethanol.** PYY antibody injected intracisternally (460 μg/rat) did not alter the formation of gastric lesions induced by 45% ethanol in rats infused intravenously or injected intracisternally with vehicle (17.9 ± 2.1 and 17.3 ± 2.6%, respectively). PYY infused intravenously (75 pmol·kg⁻¹·h⁻¹) or injected intracisternally (24 pmol/rat) reduced ethanol-induced gastric lesions to 6.6 ± 2.3 and 7.2 ± 3.1%, respectively, in rats pretreated intracisternally with NRIgG (460 μg/rat). The protective effect of intracisternal PYY was significantly attenuated by PYY antibody injected intracisternally (12.0 ± 1.2%; P < 0.05 vs. intracisternal NRIgG), whereas that of intravenous PYY was not influenced (5.7 ± 2.8%; P > 0.05; Fig. 3).

**Effect of vagotomy on intravenous PYY-induced gastric protection against ethanol.** There was no significant difference between sham-operated and vagoto-

---

Fig. 1. Intravenous infusion of peptide YY (PYY) reduced intragastric ethanol-induced gastric lesions in urethane-anesthetized rats. PYY or vehicle (BSA/saline) was infused intravenously from 30 min before to 60 min after the intragastric ethanol (45%, 5 ml/kg) administration. Each column represents mean ± SE of number of rats indicated in the bottom of each column. *P < 0.05 compared with intravenous vehicle (dose 0) group.

Fig. 2. Effects of intravenous anti-PYY on intravenous and intracisternal PYY-induced gastric protection against intragastric ethanol in urethane-anesthetized rats. Anti-PYY or nonspecific IgG from normal rabbit (NRIgG) was injected intravenously (2 mg/rat) 10 min before intracisternal or intravenous PYY. PYY or vehicle (BSA/saline) was infused from 30 min before to 60 min after intragastric ethanol (45%, 5 ml/kg) administration; PYY or saline was intracisternally injected 30 min before the ethanol administration. The gastric lesions were assessed 60 min after the ethanol administration. Each column represents mean ± SE of number of rats indicated in the bottom of each column. *P < 0.05 compared with corresponding vehicle group; +P < 0.05 compared with NRIgG pretreatment/intravenous PYY group.

---

AJP-Gastrointest Liver Physiol • VOL 283 • NOVEMBER 2002 • www.ajpfi.org
mized groups in the formation of gastric lesions induced by intragastric ethanol in intravenous vehicle-infused rats. Bilateral cervical vagotomy did not influence intravenous PYY (75 pmol·kg⁻¹·h⁻¹)-induced gastric protection against 45% ethanol (Table 1).

Effects of intravenous NPY/PYY analogs on ethanol-induced gastric lesions. r/p[Pro³⁴]NPY (75 pmol·kg⁻¹·h⁻¹ iv) significantly decreased 45% ethanol-induced gastric lesions to 3.5 ± 1.0% (P < 0.01) compared with 18.6 ± 3.3% in the intravenous vehicle group. In contrast, p[Leu³¹, Pro³⁴]NPY and r/pPYY-(3–36) infused at the same dose had no effect on gastric lesions (15.9 ± 3.9 and 22.5 ± 4.3%, respectively; Fig. 4).

Table 1. Effect of bilateral cervical vagotomy on intravenous PYY induced gastric protection against intragastric ethanol

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BSA/saline (1 ml/h iv)</th>
<th>PYY (75 pmol·kg⁻¹·h⁻¹ iv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham operation</td>
<td>19.1 ± 1.5</td>
<td>6.8 ± 1.1*</td>
</tr>
<tr>
<td>Vagotomy</td>
<td>18.3 ± 1.8</td>
<td>5.9 ± 0.7*</td>
</tr>
</tbody>
</table>

Values are means ± SE of 5 rats in each group. Urethane-anesthetized rats were subjected to sham operation or bilateral cervical vagotomy and were infused intravenously with vehicle (BSA/saline) or peptide YY (PYY) from 30 min before to 60 min after intragastric administration of 45% ethanol (5 ml/kg). Rats were euthanized 60 min after ethanol administration, and gastric lesions were monitored. *P < 0.05 compared with corresponding BSA/saline group.

DISCUSSION

The present study showed 1) that r/pPYY infused intravenously and injected intracisternally exerts a gastroprotective effect against intragastric administration of 45% ethanol-induced mucosal lesions in urethane-anesthetized rats; 2) PYY antibody injected intravenously prevented the gastric protective effect of intravenous but not intracisternal administration of PYY; 3) the gastroprotective action of intravenous PYY is independent of the vagal pathway; and 4) r/p[Pro³⁴]PYY decreased the formation of gastric lesions induced by intragastric administration of 45% ethanol, whereas p[Leu³¹, Pro³⁴]NPY and r/pPYY-(3–36) infused at the same dose had no effect.

It is well established that PYY is released from the distal ileum after a meal in various species and in humans (36). In conscious rats, PYY postprandial plasma values rise to peak levels of 75–160 pmol/l at 30–60 min, then decline to basal levels within 2–3 h depending on the meal composition and the mode of administration (intraduodenal or intragastric) (4, 11, 19). Doses of exogenous PYY reproducing postprandial levels have been reported to be 50 pmol·kg⁻¹·h⁻¹ in conscious rats and 120 pmol·kg⁻¹·h⁻¹ in urethane-anesthetized rats (19, 34). In the present study, PYY infused intravenously at 25 and 75 pmol·kg⁻¹·h⁻¹ significantly reduced gastric injury by 36 and 59%, respectively, in urethane-anesthetized rats. Although circulating levels of PYY were not measured, the doses of intravenous PYY inducing gastroprotection were within the range reported to reproduce postprandial circulating levels of PYY (4, 11, 19, 34). Immunoneutralization with specific PYY antibody has been used to establish the physiological actions of PYY on gut function (6, 22). We showed that the intracisternal or in-
intravenous injection of antibody against r/pPYY in fasted, urethane-anesthetized rats did not influence gastric lesions in response to intragastric administration of 45% ethanol. This suggests that endogenous PYY did not modulate the resistance of the gastric mucosa to injury induced by ethanol under these conditions. These data may be related to the low levels of circulating PYY reported to be around 7 pmol/l in fasted urethane-anesthetized rats (4, 34).

We previously reported that intracisternal PYY-induced gastroprotection against intragastric administration of 45% ethanol is mediated by vagal cholinergic pathways and peripheral CGRP and NO mechanisms (41). There is evidence that 125I-labeled PYY infused intravenously at doses mimicking plasma concentrations measured after a meal results in a dense representation of 125I-labeled PYY binding sites in the medullary area, solely in brain nuclei regulating gastric functions through the vagus nerve, such as the area postrema and the DVC (18, 25). In addition, we reported that the inhibition of central vagally stimulated gastric acid secretion induced by intravenous infusion of PYY is mediated by a peptide action at medullary sites (42). These findings suggest that the gastric protection induced by intravenous infusion of PYY may be mediated through central vagal-dependent pathways. However, the present findings do not support such a contention. Bilateral cervical vagotomy did not influence the gastric protection induced by intravenous PYY, providing evidence that vagal afferent and efferent signaling pathways are not involved in the gastroprotective effect. This contrasts with the gastroprotection induced by intracisternal PYY that is mediated by muscarinic-dependent mechanisms (41). In addition, intracisternal injection of PYY antibody (460 μg/rat) did not influence intravenous PYY (75 pmol⋅kg⁻¹⋅h⁻¹) induced-gastric protection. The lack of effect of the PYY antibody injected intracisternally is unlikely to be related to the inadequate access of the PYY antibody to the area postrema and portion of the nucleus of the solitary tract with fenestrated capillaries reached by circulating PYY (14, 18). In previous studies, the same PYY antibody (#9153) injected intracisternally at a lower dose (280 μg/rat) than used in the present study abolished the gastric antisecretory effect of PYY infused intravenously at a supraphysiologic dose (1 nmol⋅kg⁻¹⋅h⁻¹) (42). Moreover, the intracisternal injection of the PYY antibody (460 μg/rat) blunted intracisternal PYY-induced reduction of ethanol injury, whereas intracisternal injection of NR-IgG had no effect. The partial prevention (52%) of the gastroprotective effect of intracisternal PYY by intracisternal PYY antibody may be related to the insufficient immunoneutralization due to the limitation to IgG concentration within the small volume used for intracisternal injection. The present data also showed that intravenous injection of PYY antibody did not modify the intracisternal PYY-induced-gastric protection while blocking the gastric protective effect of intravenous PYY. These data indicate that intracisternal PYY-induced reduction of gastric lesions is not exerted peripherally as a result of peptide leakage from the cerebrospinal fluid into the systemic circulation (38), supporting that intracisternal PYY acts centrally to reduce gastric erosions (20, 41). Together, previous and present findings support distinct mechanisms for intravenous and intracisternal PYY-induced gastroprotection against ethanol injury.

It is now widely accepted that NPY/PYY/PP binds to and activates at least six Y-receptor subtypes (5). Insight to the Y-receptor subtype(s) mediating a specific NPY/PYY/PP action can be obtained by the use of prototypic NPY/PYY agonists with differential binding affinities for the Y-receptor subtypes. PYY has a strong affinity for Y₁, Y₂, and PYY-prefering receptor subtypes (5). [Pro³⁴]PYY is a preferential agonist at Y₁ and PYY-prefering receptors, whereas [Leu³¹, Pro³⁴]NPY is an agonist at Y₁/Y₃/Y₅ and PYY-(3–36) is an agonist at Y₂-receptor subtypes (15, 23). In the present study, r/p[Pro³⁴]PYY infused intravenously (75 pmol⋅kg⁻¹⋅h⁻¹) induced similar gastric protective action as that induced by the maximal effective dose of PYY. By contrast, intravenous infusion of p[Leu³¹, Pro³⁴]NPY or r/pPYY-(3–36) had no effect. These findings suggest that intravenous PYY-induced gastroprotection against intragastric ethanol is preferentially mediated via the activation of PYY-prefering receptors. Dose-response studies with PYY infused intravenously showed a linear dose-related response resulting in a 36 and 59% reduction of gastric lesions at 25 and 75 pmol⋅kg⁻¹⋅h⁻¹, respectively, whereas at 125 or 250 pmol⋅kg⁻¹⋅h⁻¹, PYY tends to be less efficient (40 and 38% reduction, respectively) than at 75 pmol⋅kg⁻¹⋅h⁻¹. The lack of linear dose response at the highest doses may be related to the activation of other Y receptors having opposite actions on gastric mucosa injured by ethanol. It is of note that the Y₂ preferential agonist PYY-(3–36) infused intravenously at 75 pmol⋅kg⁻¹⋅h⁻¹ shows a tendency to increase ethanol-induced gastric lesions. Previous studies indicate that Y₁/PYY-prefering and Y₂ receptors can exert opposite effects on gastric function (8, 40).

The peripheral mechanisms through which intravenous PYY induces gastroprotection via vagal independent pathways are still to be elucidated. It is unlikely to be secondary to intravenous PYY-induced changes in gastric acid secretion. First, we previously showed that the dose-related inhibition of vagally stimulated gastric acid secretion induced by intravenous infusion of PYY in urethane-anesthetized rats occurred at higher doses (0.25–1 nmol⋅kg⁻¹⋅h⁻¹) (42) than those reducing ethanol-induced gastric lesions (25–75 pmol⋅kg⁻¹⋅h⁻¹) in the present study. Second, vagotomy that inhibits gastric acid secretion did not influence the gastroprotective action of intravenous PYY. Third, several reports indicate that gastric lesions induced by ethanol are not influenced by antisecretory treatments (33, 46). The intravenous infusion of PYY-induced gastroprotection against intragastric ethanol is also unlikely to be secondary to alterations of gastric emptying of ethanol administered intragastrically. Studies (32) in conscious rats showed that there is no change in gastric emptying after intraperitoneal injection of PYY at a dose 17-fold higher than that
used in the present study and at 4 nmol/kg, PYY reduced gastric emptying of a liquid by 52%. Moreover, pylorus ligation, which prevents gastric emptying, did not influence the percentage of gastric erosions induced by intragastric ethanol administration (46). Existing evidence also does not suggest a mediation of the intravenous PYY gastroprotective action through the release of gut peptides known to influence ethanol-induced gastric lesions (9, 21). In dogs, PYY infused at a dose that strongly inhibited the cephalic phase of gastric acid secretion did not influence the release of gut peptides, including gastrin, somatostatin, secretin, gastric inhibitory polypeptide, PP, and neurotensin (12, 17, 39). In isolated, vascularly perfused rat stomach, PYY perfused at concentrations of 10 pM to 100 nM did not change somatostatin secretion (10, 13). Further investigations as to whether PYY influences gastric CGRP and NO pathways may provide valuable information on the peripheral mechanisms of PYY gastroprotective functions. There is evidence for the presence of a 65-kDa cell surface receptor that binds to PYY on the epithelial cells of the stomach, duodenum, and intestine (27). The possible action through these receptors needs to be investigated.

In summary, PYY infused intravenously at doses reproducing reported postprandial plasma levels induces a gastroprotective effect against ethanol lesions that is independent of the vagus nerve and not altered by central injection of PYY antibody. The intracranial injection of PYY also induced gastric protection, which is blunted by PYY antibody injected intracranially, whereas intravenous PYY antibody selectively blocked intravenous but not intracranial PYY-induced gastroprotection. The use of prototypic PYY/NPY agonists at Y receptors indicates that the action of intravenous PYY is mediated by PYY-prefering receptors. These results suggest that PYY released after a meal may exert a physiological role to increase the resistance of the gastric mucosa to injury.

We thank Dr. J. Rivier (Clayton Foundation Laboratories for Peptide Biology, Salk Institute, La Jolla, CA) for the supply of r/pPYY, r/pPYY3–36, and P. Kirsh for assistance in preparing the manuscript.

This work was supported by National Institute of Diabetes and Digestive and Kidney Diseases Grants DK-30110 (to Y. Taché) and DK-41301 (to CURE/DDRC Animal Core, Antibody Core and Peptide Core).

REFERENCES


AJP-Gastrointest Liver Physiol • VOL 283 • NOVEMBER 2002 • www.ajpgi.org


