Centrally administered neuropeptide Y delays gastric emptying via Y₂ receptors in rats

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Ishiguchi, Tadashi, Taku Amano, Hiroki Matsubayashi, Hitoshi Tada, Mikio Fujita, and Toku Takahashi. Centrally administered neuropeptide Y delays gastric emptying via Y₂ receptors in rats. Am J Physiol Regulatory Integrative Comp Physiol 281: R1522–R1530, 2001.—It has been shown that centrally administered neuropeptide Y (NPY) delays gastric emptying. To determine the receptor subtypes of NPY mediating the inhibitory effects on gastric emptying, effects of intracerebroventricular injection of NPY, [Leu³¹,Pro³⁴]NPY (a Y₁ agonist) and NPY-(3–36) (a Y₂ agonist) on solid gastric emptying and postprandial antropyloric motility were studied in conscious rats. Intracerebroventricular injection of NPY and NPY-(3–36), but not [Leu³¹,Pro³⁴]NPY, delayed solid gastric emptying in a dose-dependent manner (0.03–3 nmol). After the feeding (40 min), contractions with low frequency and high amplitude of the antrum were frequently observed, and the peak contraction of the antrum occurred most often 3–6 s before the peak contraction of the pylorus. Intracerebroventricular injection of NPY and NPY-(3–36) (3 nmol), but not [Leu³¹,Pro³⁴]NPY, significantly reduced antral contractions and the number of antropyloric coordination events. It is suggested that centrally administered NPY impairs postprandial antral contractions and antropyloric coordination via Y₂ receptors, resulting in delayed gastric emptying.

anorexia nervosa; dorsal vagal complex; migrating motor complex; vagus nerve

NEUROPEPTIDE Y (NPY) is a 36-amino-acid peptide isolated originally from porcine brain (25). NPY is the most potent known stimulant of feeding and is present in high concentrations in the central nervous system, particularly in the hypothalamus, limbic brain regions, cerebral cortex, and various brain stem nuclei (11). It has been shown that the central NPY plays a role in modulation of upper gastrointestinal myoelectrical activity (3, 5, 28, 29).

NPY levels in cerebrospinal fluid are elevated in patients with anorexia nervosa (14), and gastric emptying is delayed in these patients (12). It has been shown that intracisternally administered NPY elicits the suppression of gastric emptying of both solid and liquid meals (17). However, the precise mechanism of delayed gastric emptying induced by centrally administered NPY remains unclear.

Six recognized subtypes of NPY receptors have been described (Y₁–Y₆) using segments and analogs of NPY. Two of these, Y₁ and Y₂ receptors, are both found in large quantities in the dorsal vagal complex (DVC) of the medulla. Y₁ and Y₂ receptors are found both pre- and postjunctionally in the nervous system. Chen et al. (3) have shown that a Y₂ agonist applied to the DVC suppressed gastric motility in thyrotropin-releasing hormone (TRH)-stimulated conditions. In contrast, a Y₁ agonist had no effect on TRH-stimulated gastric motility.

In the present study, we studied the effect of intracerebroventricular injection of NPY, [Leu³¹,Pro³⁴]NPY (a Y₁ agonist), and NPY-(3–36) (a Y₂ agonist) on gastric emptying to elucidate which NPY receptor subtype is involved in mediating gastric emptying. Because antropyloric coordination is a crucial factor for the regulation of solid gastric emptying, we also studied the effect of intracerebroventricular injection of NPY and its analogs on postprandial antropyloric coordination in conscious rats.

METHODS

Gastric emptying study. All animal experiments were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Every effort was made to minimize animal suffering and reduce the number of animals used.

Male Sprague-Dawley rats (body wt 230–250 g) were kept on a 12:12-h light-dark cycle (0800–2000) with free access to chow and water. Rats were fasted overnight and were anesthetized with an intramuscular injection of xylazine and ketamine (13 and 87 mg/kg, respectively). Rats were placed in a stereotaxic apparatus, and a guide cannula made from 24-gauge stainless steel tubing was implanted in the right ventricle. Rats were allowed to recover for 1 wk.

After 24 h of fasting, rats received intracerebroventricular injections of saline (3 μl), NPY (0.03–3 nmol/3 μl), [Leu³¹,Pro³⁴]NPY (a Y₁ agonist; 0.03–3 nmol/3 μl), or NPY-(3–36) (3 nmol) or NPY-(3–36) (3 nmol), but not [Leu³¹,Pro³⁴]NPY, delayed solid gastric emptying in a dose-dependent manner (0.03–3 nmol). After the feeding (40 min), contractions with low frequency and high amplitude of the antrum were frequently observed, and the peak contraction of the antrum occurred most often 3–6 s before the peak contraction of the pylorus. Intracerebroventricular injection of NPY and NPY-(3–36) (3 nmol), but not [Leu³¹,Pro³⁴]NPY, significantly reduced antral contractions and the number of antropyloric coordination events. It is suggested that centrally administered NPY impairs postprandial antral contractions and antropyloric coordination via Y₂ receptors, resulting in delayed gastric emptying.

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Abdominal wall was closed, and rats were allowed to recover for 4 days, a force transducer was sutured on the serosal surface of the antrum to record the circular muscle contraction. The stomach was surgically isolated and removed. The gastric content was recovered from the stomach, dried, and weighed. Solid gastric emptying was calculated according to the following formula:

\[
\text{Gastric emptying (%) } = \left[1 - \left(\frac{\text{dried weight of food recovered from stomach}}{\text{weight of food intake}}\right)\right] \times 100
\]

Recording of gastric motility in response to feeding in conscious rats. Three days after the intracerebroventricular cannulation, rats were fasted overnight and anesthetized with pentobarbital sodium (45 mg/kg ip). Two miniature force transducers were sutured on the serosal surface of the antrum and pylorus to record the circular muscle contraction. This method has been used widely to record gastric and pyloric motility in rats and cats in the last decade (9, 15). We have recently demonstrated that the pylorus showed specific motility patterns in the basal and stimulated state that were quite different from those of the antrum and duodenum in rats in vivo (13). The wires to transducers were run under the skin to an opening made in the back of the neck using a rat protective system (Star Medical, Tokyo, Japan). The abdominal wall was closed, and rats were allowed to recover for 4 days.

After 24 h of fasting, rats were given 1.5 g of rat chow. Gastric motility was observed at least 120 min after the feeding. During the experiments, the wires from transducers were connected to a recording system. The area under the curve was calculated using a computer-assisted system (Mac Lab; ADInstruments, Castle Hill, Australia) and was expressed as a motility index. The motility index was evaluated before and after the feeding.

The motility of the antrum and pylorus was first studied under intracerebroventricular injection of saline (control experiment). On a different day, the same rat received intracerebroventricular injections of NPY (3 nmol/3 μl), [Leu^{31,Pro^{34}}]NPY (3 nmol/3 μl), or NPY-(3–36) (3 nmol/3 μl) 30 min before feeding. The motility of the antrum and pylorus in response to feeding or sham feeding was compared among rats that received intracerebroventricular injections of saline, NPY, [Leu^{31,Pro^{34}}]NPY, and NPY-(3–36) (3 nmol/3 μl) had no effects on food intake for 10 min.

As shown in Fig. 2, intracerebroventricular injection of NPY (3 nmol) caused a significant contraction in conscious rats. To investigate whether central effects of NPY on gastric motility were the result of leakage from the cerebrospinal fluid in the bloodstream, three rats received an intracerebroventricular injection of [Leu^{31,Pro^{34}}]NPY (3 nmol/3 μl), NPY-(3–36) (3 nmol/3 μl), or NPY-(3–36) (3 nmol/3 μl). An intracerebroventricular injection of NPY (0.03–3 nmol) delayed solid gastric emptying in a dose-dependent manner (P = 8.10, degrees of freedom (df) = 3.18, P = 0.013, n = 5). An intracerebroventricular injection of NPY-(3–36) (0.03–3 nmol) also delayed gastric emptying in a dose-dependent manner (F = 20.59, df = 3.18, P = 0.0001, n = 5). In contrast, an intracerebroventricular injection of [Leu^{31,Pro^{34}}]NPY had no significant effects on gastric emptying (n = 5; Fig. 1).

Effects of intracerebroventricular injection of NPY, [Leu^{31,Pro^{34}}]NPY, and NPY-(3–36) on solid gastric emptying. As shown in Table 1, preadministration of saline (3 μl), NPY, [Leu^{31,Pro^{34}}]NPY, and NPY-(3–36) (3 nmol/3 μl) had no effects on food intake for 10 min.

The solid gastric emptying was 65.2 ± 3.4% in rats that received intracerebroventricular injection of saline (3 μl; n = 7). An intracerebroventricular injection of NPY (0.03–3 nmol) delayed solid gastric emptying in a dose-dependent manner (P = 8.10, degrees of freedom (df) = 3.18, P = 0.013, n = 5). An intracerebroventricular injection of NPY-(3–36) (0.03–3 nmol) also delayed gastric emptying in a dose-dependent manner (F = 20.59, df = 3.18, P = 0.0001, n = 5). In contrast, an intracerebroventricular injection of [Leu^{31,Pro^{34}}]NPY had no significant effects on gastric emptying (n = 5; Fig. 1).

Effects of intracerebroventricular injection of NPY, [Leu^{31,Pro^{34}}]NPY, and NPY-(3–36) on spontaneous motility of the antrum and pylorus in the fasting state. Intracerebroventricular injection of NPY (3 nmol) and NPY-(3–36) (3 nmol) significantly increased spontaneous motility of the antrum and pylorus.

Table 1. Food intake after icv injection of saline, NPY, [Leu^{31,Pro^{34}}]NPY, and NPY-(3–36) for 10 min

<table>
<thead>
<tr>
<th>Food Intake, g</th>
<th>Saline (3 μl)</th>
<th>NPY (3 nmol)</th>
<th>[Leu^{31,Pro^{34}}]NPY (3 nmol)</th>
<th>NPY-(3–36) (3 nmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.28 ± 0.05</td>
<td>1.27 ± 0.04</td>
<td>1.22 ± 0.05</td>
<td>1.29 ± 0.03</td>
</tr>
</tbody>
</table>

Values are means ± SE; for 6 rats in each group. NPY, neuropeptide Y.
ous motility of the antrum and pylorus. Intracerebroventricular injection of NPY and NPY-(3–36) changed the antral motility from the fasting pattern to the fed pattern (Fig. 2, B and D). In contrast, intracerebroventricular injection of [Leu\textsuperscript{31},Pro\textsuperscript{34}]NPY had no effect on spontaneous contractions in the antrum or pylorus (Fig. 2C). The motility index of the antrum for 1 h was significantly increased with NPY (194 \pm 632% increase of basal, n = 6, P = 0.038) and NPY-(3–36) (156 \pm 21% increase of basal, n = 6, P = 0.014), but not with [Leu\textsuperscript{31},Pro\textsuperscript{34}]NPY (93 \pm 11% increase of basal, n = 6), compared with the saline-injected group (98 \pm 3% increase of basal, n = 6). The motility index of the pylorus for 1 h was also significantly increased by NPY-(3–36) (225 \pm 38% increase of basal, n = 6, P = 0.015) but not with [Leu\textsuperscript{31},Pro\textsuperscript{34}]NPY (95 \pm 6% increase of basal, n = 6), compared with the saline-injected group (95 \pm 12% increase of basal). The motility index of the pylorus for 1 h tended to increase with NPY (136 \pm 25% increase of basal, n = 6, P = 0.08) compared with the saline-injected group.

In contrast, the spontaneous motility index of the antrum (1,689 \pm 350 g/s for 10 min, n = 3) was not significantly affected after the intravenous infusion of NPY (3 nmol: 1,845 \pm 395 g/s for 10 min, n = 3; Fig. 3). This suggests that the stimulatory effects of intracerebroventricular injection of NPY on gastric motility were not the result of leakage from the cerebrospinal fluid in the bloodstream.

Effects of intracerebroventricular injection of NPY, [Leu\textsuperscript{31},Pro\textsuperscript{34}]NPY, and NPY-(3–36) on gastric motility in response to feeding. In saline-injected rats, feeding of rat chow immediately caused significant phasic contractions of the antrum and pylorus. These contractions were sustained for up to 10 min after feeding, and this period seems to reflect the grinding process of the gastric content. Both the antrum and pylorus contracted randomly in this period (Fig. 4A).

**Fig. 1.** Effects of icv injection of neuropeptide Y (NPY; ○), [Leu\textsuperscript{31},Pro\textsuperscript{34}]NPY (▲), and NPY-(3–36) (●) on gastric emptying. An icv injection of NPY (0.03–3 nmol) and NPY-(3–36) (0.03–3 nmol) delayed solid gastric emptying in a dose-dependent manner, whereas [Leu\textsuperscript{31},Pro\textsuperscript{34}]NPY had no effect on gastric emptying (n = 5–7).

**Fig. 2.** Effects of icv injection of saline (3 \(\mu\)l; A), NPY (3 nmol/3 \(\mu\)l; B), [Leu\textsuperscript{31},Pro\textsuperscript{34}]NPY (3 nmol/3 \(\mu\)l; C), and NPY-(3–36) (3 nmol/3 \(\mu\)l; D) on spontaneous motility. An icv injection of NPY and NPY-(3–36) significantly increased spontaneous motility of the antrum and pylorus. The migrating motor complex (MMC) was not observed after icv injection of NPY and NPY-(3–36). In contrast, icv injection of [Leu\textsuperscript{31},Pro\textsuperscript{34}]NPY had no effect on basal contraction and MMC of the antrum and pylorus.

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After the feeding (40 min), the contractile pattern of the antrum changed significantly. Contractions with low frequency (<3 cycles/min) and high amplitude (>20 g) of the antrum were frequently observed in this period (Figs. 4A and 5). This period seems to reflect the emptying process of the gastric content, and the coordination between the antrum and pylorus was frequently observed. The peak contraction of the antrum occurred most often 3–6 s (3.9 ± 0.5 s) before the peak contraction of the pylorus (Figs. 4A and 5). The number of episodes of coordination between the antrum and pylorus was significantly increased at 40–80 min after the feeding (Table 2).

Intracerebroventricular injection of NPY (3 nmol) and NPY-(3–36) (3 nmol) significantly reduced feeding-induced antral contractions in the emptying period (Fig. 4, B and D) compared with the saline-injected group (Fig. 4A). In contrast, intracerebroventricular injection of [Leu31,Pro34]NPY had no significant effects on feeding-induced antral contractions in the emptying period (Fig. 4C). The calculated motility index of the antrum was significantly reduced by intracerebroventricular injection of NPY (P < 0.01, n = 6) and NPY-(3–36) (P < 0.01, n = 6) in the emptying period compared with the saline-injected group (Fig. 6A). The number of episodes of antropyloric coordination was...
significantly reduced by intracerebroventricular injection of NPY and NPY-(3–36) in the emptying period (40–60 min after the feeding; Table 2). In contrast, intracerebroventricular injection of [Leu31,Pro34]NPY had no effect on antropyloric coordination in response to feeding (Table 2).

The motility index of the pylorus in response to feeding was not significantly affected by intracerebroventricular injection of NPY, NPY-(3–36), or [Leu31,Pro34]NPY in the emptying period (Figs. 4 and 6B).

Effects of intracerebroventricular injection of NPY, [Leu31,Pro34]NPY, and NPY-(3–36) on gastric motility in response to sham feeding. Sham feeding immediately caused significant phasic contractions in both the antrum and pylorus in saline-injected rats (Fig. 7A). Sham feeding-induced contractions of the antrum were significantly reduced by intracerebroventricular injection of NPY (3 nmol; \( P < 0.01, n = 6 \)) and NPY-(3–36) (3 nmol; \( P < 0.01, n = 6 \); Fig. 7, B, D, and E). Sham feeding-induced pyloric contractions were also significantly reduced by intracerebroventricular injection of NPY (\( P < 0.01, n = 6 \)) and NPY-(3–36) (\( P < 0.05, n = 6 \); Fig. 7, B, D, and E). In contrast, sham feeding-induced contractions were not affected by intracerebroventricular injection of [Leu31,Pro34]NPY in the antrum or pylorus (Fig. 7, C and E).

Table 2. The number of episodes of antropyloric coordination after icv injection of saline, NPY, [Leu31,Pro34]NPY, and NPY-(3–36)

<table>
<thead>
<tr>
<th>Time After Feeding, min</th>
<th>0–20</th>
<th>20–40</th>
<th>40–60</th>
<th>60–80</th>
<th>80–100</th>
<th>100–120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline (3 μl)</td>
<td>1.9 ± 0.6</td>
<td>6.5 ± 2.4</td>
<td>8.6 ± 1.8</td>
<td>6.5 ± 2.9</td>
<td>4.4 ± 2.1</td>
<td>2.5 ± 1.0</td>
</tr>
<tr>
<td>NPY (3 nmol)</td>
<td>2.6 ± 1.4</td>
<td>2.3 ± 0.8</td>
<td>1.3 ± 0.9*</td>
<td>1.7 ± 0.8</td>
<td>0.5 ± 0.2</td>
<td>0</td>
</tr>
<tr>
<td>[Leu31,Pro34]NPY (3 nmol)</td>
<td>2.3 ± 0.9</td>
<td>8.6 ± 0.7</td>
<td>10.3 ± 2.3</td>
<td>5.8 ± 1.3</td>
<td>6.8 ± 3.5</td>
<td>5.3 ± 3.8</td>
</tr>
<tr>
<td>NPY-(3–36) (3 nmol)</td>
<td>2.4 ± 0.9</td>
<td>3.8 ± 2.0</td>
<td>1.4 ± 0.5*</td>
<td>2.0 ± 1.1</td>
<td>2.0 ± 0.9</td>
<td>1.5 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SE for 6 rats in each group. No. of episodes of antropyloric coordination was significantly reduced by icv injection of NPY and NPY-(3–36) but not by [Leu31,Pro34]NPY 40–60 min after the feeding, *\( P < 0.0001, F = 17.22 \), degrees of freedom = 3,15.
DISCUSSION

The emptying of liquids from the stomach is thought to be primarily a function of the pressure gradient between the stomach and the duodenum. Intragastric pressure is generated by gastric contractions, mainly from the proximal stomach (18). Therefore, it is generally accepted that gastric emptying of liquids seems to reflect mainly fundal activity. Although the role of the pylorus in regulating liquid gastric emptying is not well understood, it has been demonstrated that pulsatile transpyloric flow of the liquids in the duodenum occurs predominantly during the nonlumen occlusive stage of propagated gastric contractions (1).

On the other hand, it has been generally accepted that solid gastric emptying is regulated by the coordination of the antrum, pylorus, and duodenum (7, 18). The antral pump and pyloric opening are of paramount importance for emptying solids. Large solid particles are retained in the stomach by the pyloric closure and are retropelled and triturated in the antral mill (2, 18).

In our present study, feeding of rat chow immediately caused significant contractions of the antrum and pylorus in conscious rats. These contractions were sustained up to 10 min after feeding; this period seems to reflect the grinding process of the gastric content. Both the antrum and pylorus contracted randomly in this period. In contrast, the contractile pattern of the antrum was changed significantly 40 min after the feeding. Contractions with low frequency and high amplitude of the antrum were frequently observed 40 min after the feeding. Contractions with low frequency and high amplitude of the antrum were frequently observed in this period; this period seems to reflect the emptying process of the gastric content. Therefore, it is suggested that the antrum and pylorus act differently between the grinding period and emptying period after the feeding. Our observation is consistent with the previous study by Brown et al. (2), who divided the postprandial state of the human stomach into the following three stages: early postprandial state, intermediate state, and late postprandial state. Using real-time ultrasound images, they demonstrated that antral motility significantly increased in the early postprandial state and decreased in the late postprandial state. The distal antrum participated in grinding of large particles by changing its configuration to a tubular shape (2).

Various types of patterns of coordination between the antrum and pylorus were observed in the emptying period. The time lag was most frequently observed between each contraction of the antrum and pylorus. The contraction maxima of the antrum occurred most often 3–6 s before the contraction maxima of the pylorus. In some cases, antral contractions were frequently associated with pyloric relaxations. The coordination between the antrum and pylorus seems to be effective to propel the gastric contents to the duodenum. The episodes of coordinated antropyloric contractions, which have not been observed within 20 min after feeding, significantly increased 40–60 min after feeding. This suggests that coordinated antropyloric contractions observed at 40–60 min after feeding play an important role for the gastric emptying of solids in rats.

It has been shown that intracisternally administered NPY elicits the suppression of gastric emptying of both solid and liquid meals (17). We have also shown that intracerebroventricular injection of NPY (0.03–3 nmol) significantly delayed solid gastric emptying in conscious rats.

NPY is a powerful stimulant of food intake. Gerald et al. (6) demonstrated that intracerebroventricular injection of NPY (0.3 nmol) significantly increased food intake in rats from 0.4 to 3.3 g when food was given for 4 h in the nonfasted state. In contrast, our current study has shown that intracerebroventricular injection of NPY (3 nmol) had no significant effects on food intake (1.25 g) compared with that of saline-injected rats (1.27 g) when food was given for 10 min after 24 h of fasting. This suggests that stimulatory effects of
NPY on food intake may depend on the fasting condition and the duration of food intake.

In the brain, NPY binding sites are seen in a variety of areas, including the cortex, hypothalamus, pons, and medulla oblongata. Results from binding studies have characterized six distinct subtypes of receptors. Two of these, Y1 and Y2, are both found in large quantities in the DVC of the medulla. Y1 and Y2 receptors are found both pre- and postjunctionally in the nervous system (3, 11, 20, 28). In contrast, it is suggested that NPY activates a hypothalamic feeding center via Y5 receptors (6).

There appears to be different effects after either stimulation or inhibition of NPY receptor subtypes, especially Y1 and Y2 (3, 20). Microinjection of NPY and a Y1 agonist in DVC increased bile secretion in a dose-dependent manner in anesthetized rats. In contrast, microinjection of a Y2 agonist inhibited bile secretion (28, 29).

We have shown that intracerebroventricular injections of NPY and a Y2 agonist, not a Y1 agonist, significantly impaired antral contractions and antropyloric coordination in the emptying period. Because our recent study has shown that feeding-induced antral contractions in the emptying period were significantly reduced in vagotomized rats (unpublished observations), it is conceivable that Y2 receptor stimulation may inhibit vagal-mediated events.

Many central nervous system peptides, including NPY, act via vagal mechanisms (23). In urethan-anesthetized rats, Chen et al. (3) have shown that a Y2 agonist applied to the DVC suppressed gastric motility in TRH-stimulated conditions. In contrast, a Y1 agonist had no effect on TRH-stimulated gastric motility.

It is well established that sham feeding-induced gastric contraction is mediated via the vagal pathway (22). Sham feeding immediately caused the contraction of the pylorus and antrum in control rats. Sham feeding-induced contraction was abolished by pretreatment with atropine (50 μg/kg; data not shown), confirming mediation of the cholinergic pathway. Sham feeding-induced contraction of the antrum and pylorus was reduced significantly by intracerebroventricular...
injection of NPY and a Y2 agonist. These results strongly suggest that Y2 receptor stimulation inhibits vagal activity. Because agents injected in the lateral ventricle may act in the forebrain, we cannot exclude the possibility that NPY and Y2 agonists may have distinct effects on gastric emptying via forebrain sites of action.

It has been shown that centrally administered NPY inhibits the migrating motor complex (MMC) in the canine stomach (26). Similarly, we have shown that intracerebroventricular administration of NPY and a Y2 agonist changed the antral motility from the fasting pattern to the fed pattern in conscious rats. Vagal blockade by cooling has been shown to reversibly inhibit MMC activity in the stomach in conscious dogs (4, 8). In contrast, the small bowel exhibited MMC-like migrating bursts of spikes in both the fasted and fed states during vagal blockade in conscious dogs (4). In addition, vagal blockade significantly increased pyloric contractions (21). Thus it is conceivable that centrally administered NPY may inhibit the vagal pathway innervating to stomach, resulting in inhibition of gastric MMC.

On the other hand, it has been demonstrated recently that centrally administered NPY induces duodenal MMC in rats (5). Tohara et al. (27) have shown that local intra-arterial infusion of xylocaine in the jejenum induces phase III contraction, suggesting that intestinal MMC is inhibited by the intestinal contents, which ceases the transmission from the sensory nerve endings to the inhibitory motor neurons. The initiation of the spontaneous occurrence of phase III in the digestive jejenum is likely to be brought by a temporary lack of intraluminal contents (27). Fujimiya et al. (5) have recently demonstrated that intracerebroventricular injection of NPY and a Y2 agonist converted the postprandial motility pattern into an interdigestive pattern of the rat duodenum. We have shown that NPY and a Y2 agonist significantly provoked tonic and phasic contractions of the pylorus. The stimulatory effects of NPY and a Y2 agonist on duodenal MMC (5) might be explained as the result of significant pyloric contractions by NPY and a Y2 agonist. Vacant duodenum resulting from the occlusion of the pylorus induced by NPY and a Y2 agonist may induce MMC in the duodenum.

The stimulatory effects of NPY and a Y2 agonist on pyloric contractions in the fasting state remain to be elucidated. It has been shown that vagal blockade significantly increased pyloric contraction, whereas the stomach remained silent in the fasting state in conscious dogs (21), suggesting the presence of potent inhibitory vagal inputs on the pylorus. It has been demonstrated that vagal stimulation regulates the release of nitric oxide (NO) from the gastric myenteric plexus, which mediates nonadenergic, noncholinergic (NANC) relaxations and accommodation reflex of the stomach (19, 24). We have also shown that vagal nerve stimulation caused significant NANC relaxations of the rat pylorus and that NANC relaxations were inhibited by an NO synthesis inhibitor (13). This indicates that the vagus nerve innervates NO-producing neurons in the myenteric plexus of the rat pylorus. It is conceivable that the inhibitory vagal pathway innervating the pylorus is negatively regulated via a Y2 receptor. Y2 receptor stimulation reduces the vagal inhibitory pathway, resulting in tonic and phasic contractions of the pylorus.

Feeding immediately caused phasic contractions of the antrum and pylorus. Feeding-induced contraction of the antrum and pylorus in the grinding period was slightly but not significantly reduced by NPY and a Y2 agonist. It has been shown that the gastric response within 10 min after feeding is mediated via a vagal pathway and a nonvagal (local and/or spinal) pathway. It is likely that NPY and a Y2 agonist may not inhibit the nonvagal pathway.

Intracerebroventricular injection of NPY and a Y2 agonist significantly reduced feeding-induced antral contractions in the emptying period, although they had no effects on pyloric contractions. It is suggested that the vagal efferent pathway to the antrum is more influenced than that to the pylorus by a Y2 receptor.

In conclusion, centrally administered NPY impairs postprandial gastric motility and antropyloric coordination and delays gastric emptying via a Y2 receptor. Elevated levels of NPY in the cerebrospinal fluid have been reported in patients with anorexia nervosa (14). It has also been shown that gastric emptying is delayed in these patients (12). Assessment of the relative contribution of NPY receptor subtypes to the gastric emptying and antropyloric motility in patients with anorexia nervosa may help a novel therapeutic development.

Perspectives

Feeding of rat chow immediately caused significant contractions of the antrum and pylorus. These contractions may contribute to the grinding process of the gastric contents. Thus large solid particles are retained in the stomach by the pyloric closure and are retropropelled and triturated in the antrum.

In contrast, the coordinated antropyloric contractions observed 40 min after feeding may have an important role for the emptying process. We have shown that intracerebroventricular injection of a Y2 agonist significantly impaired antropyloric coordination, probably via suppressing vagal activity.

Gastrointestinal interdigestive phasic contractions are possibly linked to hunger sensations. Fujimiya et al. (5) have demonstrated that intracerebroventricular injection of a Y2 agonist converted the postprandial motility pattern into an interdigestive pattern of the rat duodenum. We have shown that a Y2 agonist significantly provoked tonic and phasic contractions of the pylorus. The occlusion of the pylorus induced by a Y2 agonist may cause a vacant duodenum and may induce MMC in the duodenum. It is conceivable that interdigestive patterns induced by a Y2 agonist might be tightly correlated with the onset of hunger sensation and feeding, leading to various cycles of hyperphagia. On the other hand, nausea and vomiting may also be
developed frequently because of pyloric closure and impaired antpyloric coordination induced by a Y2 agonist.

Hyperphagia and repetitive vomiting are common complaints in patients with anorexia nervosa. We propose that elevated NPY levels in the central nervous system (14) may explain the delayed gastric emptying and abnormal eating behavior in these patients.

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REFERENCES