Effects of central and peripheral urocortin on fed and fasted gastroduodenal motor activity in conscious rats

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Kihara, Naoki, Masaki Fujimura, Ikuo Yamamoto, Etsuro Itoh, Akio Inui, and Mineko Fujimiya. Effects of central and peripheral urocortin on fed and fasted gastroduodenal motor activity in conscious rats. Am J Physiol Gastrointest Liver Physiol 280: G406–G419, 2001.—Since few previous studies have examined the effects of urocortin on physiological fed and fasted gastrointestinal motility, we administered urocortin intracerebroventricularly (icv) or intravenously (iv) in freely moving conscious rats and examined the changes in antral and duodenal motility. Icv and iv injection of urocortin disrupted fasted motor patterns of gastroduodenal motility, which were replaced by fed-like motor patterns. When urocortin was given icv and iv in the fed state, the motor activity remained like the fed patterns but % motor index (%MI) was decreased in the antrum and increased in the duodenum. Increase in the %MI in the duodenum induced by urocortin was shown as a nonpropagated event, since the transit of nonnutrient contents in the duodenum was decreased by icv and iv injection of urocortin. Changes in the gastroduodenal motility induced by icv injection of urocortin were abolished in animals with truncal vagotomy but not altered in animals with mechanical sympathectomy, suggesting that the vagal pathway may mediate the central action of urocortin. Neither urocortin antiserum nor α-helical CRF-(9–41) affected fed and fasted gastroduodenal motility, suggesting that endogenous urocortin is not involved in regulation of basal gastroduodenal motility.

intracerebroventricular injection; intravenous injection; stomach; duodenum

UROCORTIN, A NEWLY CHARACTERIZED mammalian neuropeptide and a member of the corticotropin-releasing factor (CRF) family, acts as an endogenous ligand for the CRF receptor (58). This peptide is implicated in various functions, such as feeding suppression (50, 51), anxiety (40), and cardiovascular (44) and gastrointestinal (41) regulation. Such a variety of actions may be accounted for by a wide distribution of CRF receptor in the brain (10, 31, 32, 33, 46, 48) and peripheral organs (26, 31). The effects of centrally administered CRF on gastrointestinal functions have been widely investigated in rats (7, 11, 29, 35, 50, 53) and mice (49). Intracerebroventricular (icv) or intracisternal injection of CRF caused the inhibition of gastric emptying of nonnutrient liquid meals (7, 29, 49, 53) or nutrient solid meals (11, 28, 35, 50), yet conversely caused the stimulation of colonic transit (17, 30, 37, 59). These effects of centrally administered CRF on gastric and colonic motility were similar to abdominal surgery- (4, 5) or stress- (8, 17, 30, 37, 39, 54, 59) induced gastric ileus or colonic dysfunction. Since central administration of CRF antagonists blocked the postoperative or stress-induced alterations of gastrointestinal dysfunction, motor responses in the gut produced by stress are thought to be mediated by the endogenous CRF in the brain (17, 30, 37, 59). Peripheral administration of CRF or urocortin also inhibited gastric emptying in rats (41), mice (2, 49), and dogs (43). Recent studies indicate that urocortin binds both CRF type 1 and 2 receptors but shows a higher affinity for CRF type 2 receptor than for CRF type 1 receptor (6, 58). To examine the receptor subtypes involved in the regulation of gastrointestinal motility induced by centrally or peripherally administered CRF and urocortin, the functional potency of selective or nonselective CRF type 1 and 2 receptor antagonists in blocking the effects of agonists has been examined (35, 41). α-Helical CRF (9–41) is known as a dual antagonist to CRF type 1 and 2 receptors (14) but is more selective for CRF type 2 receptor than for CRF type 1 receptor on the basis of functional and binding studies (26, 41). In fact, CRF type 2 receptor in both brain and peripheral organs is mainly involved in the regulation of gastrointestinal motility (35, 41).

Although a number of previous studies have shown the effects of central or peripheral administration of CRF/urocortin on gastrointestinal motility, a mere transit of meals from the stomach has been used as a marker of gastric motility. It is well known that gastrointestinal motility under physiological conditions consists of fasted and fed motor patterns and that each...
of them is regulated by different mechanisms (23). In fact, previous studies have shown that centrally administered neuropeptides regulate the fed and fasted patterns of motility. Neuropeptide Y (NPY), a feeding-stimulatory peptide in the brain, induced the fasted pattern in the duodenum when given to the fed rats (15), whereasbombesin, a feeding-inhibitory peptide, induced the fed pattern in the small intestine when given to fasted dogs (20). Therefore, it seems necessary to investigate the action of CRF/urocortin, which is known as a feeding-inhibitory peptide in the brain, on the physiological fed and fasted motor activities of the gastrointestinal tract.

In the present study, urocortin was used as a ligand for CRF receptors because urocortin is known to be two- to threefold more potent than CRF in inhibiting food intake and gastric emptying (2, 41). Urocortin was given either centrally or peripherally, and the effects on the fed and fasted patterns of gastroduodenal motility were examined. Changes in the motor activity in the fed state of the duodenum induced by urocortin were assessed compared with the transit of nonnutrient duodenal contents.

MATERIALS AND METHODS

Male Wistar rats (Clea Japan, Tokyo, Japan), weighing 200–250 g at the start of the experiments, were used. Rats were housed under controlled temperature (21–24°C) and light (lights on 8:00–20:00) conditions with free access to laboratory chow pellets (CE-2; Clea Japan) and water. Care of animals was conducted in accordance with the Guide for Use of Experimental Animals (Shiga University of Medical Science).

Animal preparation. The rats were anesthetized with intraperitoneal injection of pentobarbital sodium (50 mg/kg Nembutal; Abbott Laboratories), placed in a stereotaxic apparatus, and implanted with guide cannula (25-gauge; Eicom, Kyoto, Japan), which reached the right lateral ventricle. Stereotaxic coordinates were 0.8 mm posterior to bregma, 2.0 mm right lateral to the midline, and 4.5 mm below the outer surface of the skull using a Kopf stereotaxic frame with the incisor bar set at the horizontal plane passing through bregma and lambda. The guide cannula was secured with dental cement anchored by two stainless steel screws fixed on the dorsal surface of the skull. After surgery, a dummy cannula (Eicom) was inserted into each guide cannula, and a screw cap (Eicom) was put on the guide cannula to prevent blockade. The animals were allowed to recover for at least 4 days after this operation. On the day of the experiment, a dummy cannula was replaced by a microinjection cannula (AMI-5; Eicom) connected to a polyethylene tube (PE-50, Clay Adams). The placement of the cannula was verified at the end of the experiment by injection of 10 μl dye (0.05% cresyl violet) and examination of brain slices.

At 4–6 days after the brain operation, rats were deprived of food and given free access to water for 18 h before the abdominal operation. They were anesthetized with pentobarbital sodium (50 mg/kg), and the motility recording device was implanted as follows. Two manometric catheters (3-Fr, 1 mm diameter; ATOM, Tokyo, Japan) with side holes were inserted through the gastric fistula, and tips were placed at the gastric antrum and 3 cm distal to the pylorus. Catheters were fixed at the gastric wall by purse-string suture and run subcutaneously to emerge at the crown of the neck and were secured at the animal’s skin. In some animals, a catheter (3-Fr, 1 mm diameter) was placed in the right jugular vein instead of icv cannulation, run subcutaneously to emerge at the crown with the manometric catheter, and used for intravenous (iv) administration of peptides. The catheter was filled with heparinized saline to prevent obstruction. During the first postoperative day, the animals were allowed water but no food, and the experiment was performed 1 wk after the operation. Animals were fasted 18 h before the experiment.

Icv and iv injection of peptide. Urocortin (Peptide Institute, Osaka, Japan) was dissolved with 1% acetic acid solution and frozen until use. Urocortin doses of 0.01 μg, 0.1 μg, 1 μg, and 5 μg were dissolved in saline in a 10-μl volume for ivc injection or a 0.5-μl volume for iv injection. Each dose of urocortin was administered icv through the microinjection cannula anchored in the skull or iv through the jugular vein cannula. Vehicle control was made by icv or iv injection of saline.

Measurement of gastroduodenal motility. Gastroduodenal motility was measured in two conscious, freely moving rats by the manometric method. On the day of the experiment, the manometric catheter was connected to a pressure transducer (TP-400T; Nihon Koden Kogyo, Tokyo, Japan), and the catheter was protected from biting by a flexible metal sheath and connected to the infusion swivel (dual type, 20-gauge; Instech Laboratories, Plymouth Meeting, PA) to allow free movement. The catheter was continuously infused with bubble-free 0.9% saline at a rate of 2 ml/h by a low-compliance capillary infusion system using a heavy-duty pump (CVF-3100; Nihon Koden). The data were recorded on a polygraph (RM-6100; Nihon Koden) and stored in a MacLab system (MacLab/8e, AD Instruments Pty, Power Book 2400c/240; Apple Computer).

After the sequence of typical fasted pattern of motility was observed, rats were given two pellets of laboratory chow (~8 g). After the gastroduodenal motility was ascertained to have changed into the fed pattern, icv injection of each dose of peptide was performed. In some experiments, icv injection was performed in animals that showed the fasted pattern of motility. Effects of iv injection of peptides through the jugular vein cannula were also examined. In other experiments, 50 μg of α-helical CRF-(9–41) (Sigma, St. Louis, MO) were injected icv or iv before icv injection of 5 μg urocortin or injected iv or ivc before iv injection of 5 μg urocortin.

The transit of nonnutrient duodenal contents induced by icv and iv injection of urocortin was examined. One-half milliliter of optimum cutting temperature compound (Tissue-Tek; Miles, Elkhart, IN), containing 5% toluidine blue (13), was injected through the manometric catheter inserted into the duodenum 10 min after icv or iv injection of urocortin (5 μg). The rats were killed after 20 min, and duodenal transit was measured as the distance (cm) of the most distal point of the stain from the pylorus.

Immunoneutralization of intrinsic urocortin. After the sequence of fasted or fed pattern was observed, 5 μl anti-urocortin antiserum (Yanaihara Institute, Shizuoka, Japan) or normal rabbit serum plus 5 μl saline were injected icv or iv, and the change in gastroduodenal motility was observed. In other experiments, 5 μl of anti-urocortin antiserum were injected icv or iv before icv or iv injection of urocortin in both the fasted and fed states.

Truncal vagotomy and mechanical sympathectomy. Four days before the measurement of gastroduodenal motility, either truncal vagotomy or mechanical sympathectomy was performed. Under median laparotomy on anesthetized rats, the lower part of the esophagus was exposed and the anterior and posterior branches of the vagal nerve were incised. For
the mechanical sympathectomy, the roots of celiac and superior mesenteric arteries were exposed and prevertebral ganglia between these arteries were completely removed. Sham-operated controls for vagotomy and sympathectomy were made by laparotomy on anesthetized rats. Vagotomized rats were fed by liquid diet after the operation to avoid excess distention of the stomach.

Analysis of motor activity and statistical analysis. To examine the motor activity, 10 rats were used for the measurement of normal fed and fasted patterns and 3 rats were used for each experiment. The frequency of the onset of phase III-like activities in the antrum was 5.17 ± 0.51/h (n = 6), and that in the duodenum was 5.63 ± 1.30/h (n = 6); those were in accordance with the migrating myoelectrical complex (MMC) (53). After food intake, the fasted motor pattern was disrupted and replaced by the fed motor pattern, which consisted of irregular contractions of high frequency: 3.8 ± 0.6/min (n = 10) in the stomach and 1.8 ± 0.6/min (n = 10) in the duodenum. Such fed motor patterns continued for 109.0 ± 7.8 min (n = 5) in the stomach and 119.0 ± 30.9 min (n = 5) in the duodenum, followed by the onset of the phase III-like activities (Fig. 1).

RESULTS

Gastroduodenal fed and fasted motor activity in conscious rats. In the fasted state, the cyclic changes of pressure waves were detected in both the antrum and duodenum by a manometric method, including the quiescence period, during which relatively low amplitude of contractions occurred (phase I-like contraction), followed by a grouping of strong contractions (phase III-like contraction) (Fig. 1). The frequency of the onset of the phase III-like activity in the antrum was 5.17 ± 0.51/h (n = 6), and that in the duodenum was 5.63 ± 1.30/h (n = 6); those were in accordance with the migrating myoelectrical complex (MMC) (53). After food intake, the fasted motor pattern was disrupted and replaced by the fed motor pattern, which consisted of irregular contractions of high frequency: 3.8 ± 0.6/min (n = 10) in the stomach and 1.8 ± 0.6/min (n = 10) in the duodenum. Such fed motor patterns continued for 109.0 ± 7.8 min (n = 5) in the stomach and 119.0 ± 30.9 min (n = 5) in the duodenum, followed by the onset of the phase III-like activities (Fig. 1).

Effects of icv and iv injection of urocortin on fed and fasted motor activities. When icv injection of urocortin (1 and 5 μg) was given in the fasted state, the fasted pattern of motility, consisting of consecutive phase I and phase III-like contractions found in the antrum and duodenum, changed into the fed-like motor pattern of irregular contractions with high frequency (Fig. 2). The fed-like motor pattern induced by icv injection of urocortin (5 μg) continued for 171.0 ± 26.0 min (n = 3) both in the stomach and duodenum. When icv injection of urocortin (1 and 5 μg) was given in the fed state,
the motility pattern remained a fed pattern in both the antrum and duodenum (Fig. 3A); however, the %MI of the pressure waves was significantly reduced in the stomach and was significantly increased in the duodenum (Fig. 3B). Changes in the %MI of the pressure waves in the stomach and duodenum induced by different doses of icv urocortin are shown in Fig. 3B.

The effects of iv injection of urocortin on antral and duodenal motility were also examined. With the iv injection of urocortin (1 and 5 μg) given in the fasted state, the fasted motor pattern observed in the antrum and duodenum was replaced by the fed motor pattern, which continued for 146.0 ± 18.0 min (n = 3) in both the stomach and duodenum (Fig. 4). When iv injection of urocortin (5 μg) was given in the fed state, the fed motor patterns remained but the %MI was significantly reduced in the stomach and significantly increased in the duodenum (Fig. 5). Intravenous injection

Fig. 3. A: effect of icv injection of urocortin (5 μg/rat) on fed motor activity of the antrum and duodenum. The motility pattern remains a fed pattern; however, the amplitude of the pressure wave is decreased in the antrum but increased in the duodenum after icv injection of urocortin. B: comparison of %motor index (%MI) in the antrum and duodenum after icv injection of saline and various concentrations of urocortin in the fed state. Values are means ± SE from 3 animals. *P < 0.05 and **P < 0.01.

Fig. 4. Effect of intravenous (iv) injection of urocortin (5 μg/rat) on fasted motor activity of the antrum and duodenum. The fasted pattern is changed into the fed-like motor pattern after iv injection of urocortin in both the antrum and duodenum.
of 0.1 and 0.01 μg of urocortin had no effect on the gastroduodenal motility.

The transit of nonnutrient duodenal contents was measured by the toluidine blue migration induced by icv and iv injection of urocortin. Within 20 min after icv and iv injection of 5 μg urocortin, the distances migrated were 29.2 ± 3.0 cm (n = 3) and 30.2 ± 2.8 cm (n = 3), respectively. These values were significantly lower (P < 0.05) compared with icv (40.0 ± 3.4 cm, n = 3) and iv (41.2 ± 4.0, n = 3) injections of saline.

Effects of CRF receptor antagonist and urocortin antibody on urocortin-induced change in the gastroduodenal motility. To examine whether the effects of icv and iv injection of urocortin on the motor activity were mediated by CRF receptors in the brain and periphery, respectively, CRF receptor antagonist α-helical CRF-(9–41) was injected before urocortin. Changes in the pattern of gastroduodenal motility induced by icv and iv injection of urocortin during fasted states seen in Fig. 2 and Fig. 4 were antagonized by α-helical CRF-(9–41) given by the same route (Fig. 6). Similarly, changes in the pattern of gastroduodenal motility induced by icv and iv injection of urocortin during fed states seen in Fig. 3A and Fig. 5A were antagonized by α-helical CRF-(9–41) given by the same route (Fig. 7, A and C, and Fig. 8, A and C).

To rule out the possible leakage of icv-injected peptides into the systemic circulation, CRF receptor antagonist α-helical CRF-(9–41) was injected iv before icv injection of urocortin. Changes in the pattern of gastroduodenal motility induced by icv injection of urocortin during fed states seen in Fig. 3A were not altered by the systemic administration of α-helical CRF-(9–41) (Fig. 7, B and C). To rule out the possible influx of systemically injected peptide into the brain, α-helical CRF-(9–41) was injected icv before iv injection of urocortin. Changes in the gastroduodenal motility induced by iv injection of urocortin during the fed state seen in Fig. 5A were not altered by the icv injection of α-helical CRF-(9–41) (Fig. 8, B and C). A single injection of α-helical CRF-(9–41) iv or iv did not change the fed and fasted patterns of gastroduodenal motility (Figs. 6, A and B; 7, A and B; and 8, A and B).

The effects of passive immunoneutralization with urocortin antiserum on gastroduodenal motility during fasted and fed states were examined. Neither icv- nor iv-administered urocortin antiserum (5 μl) changed the fasted (Fig. 9B) and fed (Fig. 9D) patterns of gastroduodenal motility. The same volume of urocortin antiserum blocked the changes in the gastroduodenal motility induced by icv or iv injection of urocortin during fasted (Fig. 9A) and fed (Fig. 9C) states.

Involvement of the autonomic nervous system. We examined the involvement of the autonomic nervous system using rats that had received truncal vagotomy or sympathectomy. Normal fed and fasted patterns of gastroduodenal motility were not affected by the sympathectomy. The normal fed pattern was disrupted in
both antrum and duodenum in animals with truncal vagotomy, and the normal fasted pattern was also somewhat disrupted in the duodenum but was intact in the antrum in vagotomized animals (Fig. 10). When urocortin was injected icv in vagotomized animals, changes in the fasted pattern seen in Fig. 2 were completely abolished, especially in the antrum (Fig. 10A). However, changes in the fasted pattern induced by iv injection of urocortin seen in Fig. 4 were not basically altered by the vagotomy (Fig. 10B). In contrast, sympathectomy failed to alter the changes in fed and fasted motor activity induced by icv and iv injection of urocortin (data not shown).

**DISCUSSION**

In the present study, we investigated the effects of urocortin administered icv or iv on the fed and fasted motor activity of the antrum and duodenum in freely moving conscious rats. When urocortin was administered icv in the fasted state, the fasted patterns of antral and duodenal motility were disrupted and the fed-like motor patterns appeared. Similar results were obtained when urocortin was injected iv in fasted rats, in which the fasted patterns of antral and duodenal motility were replaced by the fed motor patterns. On the other hand, when urocortin was administered icv in the fed state, the motor activities in the antrum and duodenum were affected differently. Although the motor activities remained as fed patterns in both antrum and duodenum, %MI was decreased in the antrum but increased in the duodenum. Similar results were obtained when urocortin was administered iv in the fed state; the motor activity remained like fed patterns and %MI was decreased in the antrum but increased in the duodenum. The effects of icv or iv injection of urocortin on the motor activity of the gastrointestinal tract were mediated by CRF receptors in the brain or peripheral organs, since CRF receptor antagonist α-helical CRF-(9–41) injected via the same route as urocortin blocked these effects. To rule out the possible leakage of icv-injected peptide into the systemic circulation, iv injection of α-helical CRF-(9–41) was combined with icv injection of urocortin. Conversely, to rule out the possible influx of systemically injected peptide into the brain, icv injection of α-helical CRF-(9–41) was combined with the iv injection of urocortin. Results showed that iv injection of α-helical CRF-(9–41) did not alter the effects of icv-injected urocortin, and conversely icv
Fig. 7. A: effect of icv injection of α-helical CRF-(9–41) (50 μg/rat) before the icv injection of urocortin (5 μg/rat) on the fed motor activity of the antrum and duodenum. B: effect of iv injection of α-helical CRF-(9–41) (50 μg/rat) before the icv injection of urocortin (5 μg/rat) on the fed motor activity of the antrum and duodenum. Pretreatment of icv injection of α-helical CRF-(9–41) completely antagonizes the change in the motor activity induced by icv injection of urocortin seen in Fig. 3A, whereas pretreatment with iv injection of α-helical CRF-(9–41) does not alter the change in the motor activity induced by icv injection of urocortin. C: comparison of %MI in the antrum and duodenum induced by injection of saline, urocortin (icv), urocortin (icv) + α-helical CRF-(9–41) (icv), and urocortin (icv) + α-helical CRF-(9–41) (iv). Values are means ± SE from 3 animals. **P < 0.01. No significant change was found between %MI induced by saline and urocortin (icv) + α-helical CRF-(9–41) (icv) or between %MI induced by urocortin (icv) and urocortin (icv) + α-helical CRF-(9–41) (iv) in both antrum and duodenum.
Fig. 8. A: effect of iv injection of α-helical CRF-(9–41) (50 μg/rat) before the iv (5 μg/rat) injection of urocortin on the fed motor activity in the antrum and duodenum. B: effect of icv injection of α-helical CRF-(9–41) (50 μg/rat) before the iv (5 μg/rat) injection of urocortin on the fed motor activity of the antrum and duodenum. Pretreatment with iv injection of α-helical CRF-(9–41) completely antagonizes the change in the motor activity induced by iv injection of urocortin seen in Fig. 5A, whereas pretreatment with icv injection of α-helical CRF-(9–41) does not alter the change in the motor activity induced by iv injection of urocortin. C: comparison of %MI in the antrum and duodenum induced by injection of saline, urocortin (iv), urocortin (iv) + α-helical CRF-(9–41) (iv), and urocortin (iv) + α-helical CRF-(9–41) (icv). Values are means ± SE from 3 animals. **P < 0.01. No significant change was found between %MI induced by saline and urocortin (iv) + α-helical CRF-(9–41) (iv) or between %MI induced by urocortin (iv) and urocortin (iv) + α-helical CRF-(9–41) (icv) in both antrum and duodenum.
Fig. 9. A and C: effects of icv and iv injection of urocortin antibody (5 μl/rat) before the icv and iv injection of urocortin (5 μg/rat) on the fasted (A) and fed (C) motor activity in the antrum and duodenum. Pretreatment with urocortin antibody blocked the changes in the gastroduodenal motility induced by icv or iv injection of urocortin during fasted and fed states. B and D: effects of icv and iv injection of urocortin antibody (5 μl/rat) on the fasted (B) and fed (D) motor activity. Neither icv nor iv injection of urocortin antibody changed the fasted and fed patterns of gastroduodenal motility.
Fig. 9—Continued.
injection of α-helical CRF-(9–41) did not alter the effects of iv-injected urocortin. These data suggest that central and peripheral urocortin may exert actions independently through CRF receptors in the brain and peripheral organs. The possible brain nuclei responsive to icv injection of urocortin have been widely examined by the dual labeling of c-fos induction by icv urocortin and mRNA expression of CRF type 1 and 2 receptors (6). The c-fos induction site after icv injection of urocortin in the brain was widely distributed but not always parallel to the site expressing CRF type 2 receptor mRNA; however, it more or less overlapped with the site expressing CRF type 1 receptor mRNA (6). Furthermore, α-helical CRF-(9–41) itself is known to be a dual antagonist for CRF type 1 and 2 receptors (14). Since, however, evidence has been shown that α-helical CRF-(9–41) is more selective for the CRF type 2 receptor on the basis of functional and binding studies (26, 41), the effects of icv and iv injection of urocortin on the motor activity of the gastrointestinal tract obtained in the present study seem to be mediated mostly by CRF type 2 receptors in the brain and peripheral organs.

It is widely accepted that CRF is involved in the postoperative or stress-induced gastric ileus. From this point of view, in most of the previous studies that investigated the effects of centrally or peripherally administered CRF/urocortin on motor activities, emptying of gastric contents has been extensively investigated (7, 11, 28, 29, 35, 49, 50, 53). A few previous studies have examined the effects of centrally administered CRF on the gastric and duodenal contractility measured by a strain-gauge force transducer implanted in the stomach and duodenal wall in anesthetized rats (16, 21) and conscious dogs (28). In those experiments, central administration of CRF inhibited the gastric contractility in rats (16, 21) and stimulated the frequency of duodenal contractions but inhibited the percentage of propagated duodenal contractions in dogs (28). These opposite effects of CRF on the contractile activity between stomach and duodenum seen in the previous studies are consistent with the present results, in which %MI was decreased in the stomach but increased in the duodenum by icv and iv infusion of urocortin in the fed state of conscious rats. Both present and previous studies show that the increase in the contractile activity of the duodenum induced by CRF/urocortin was a nonpropagated event. In most of the previous studies that examined the effects of CRF/urocortin on the gastrointestinal motility, attention has been paid only to the postprandial movement of the gastrointestinal tracts, but motor activities in the fasting state have not been considered.

The present results demonstrated that the fasted pattern of gastroduodenal motility was disrupted by exogenously applied urocortin via icv or iv infusion. Several brain-gut peptides such as CCK, bombesin, and NPY are known as central or peripheral mediators.
that regulate the fed and fasted motor activity of the gastrointestinal tract (15, 20, 47). CCK has been suggested as a mediator that causes the disruption of MMCs, which corresponds with the fasting motility of the small intestine after a meal. Intraduodenal nutrient stimulates the release of CCK, which disrupts the MMC through peripheral CCK\textsubscript{B} receptors, and the released CCK acts on the vagal afferent fibers and induces a release of central CCK, which participates in MMC disruption through central CCK\textsubscript{A} receptors (1, 47). Both peripheral and central administration of bombesin cause the disruption of MMC (9, 45), and peripheral bombesin exerts the central actions through vagal afferent pathways (57). NPY exerts the opposite effects from CCK or bombesin; when NPY was administered icv in the fed state of rats, the fed motor pattern of the duodenum was replaced by the fasted motor pattern (15). The physiological significance of fasted motor activity in the gastrointestinal tract has been considered to be a mechanical and chemical cleansing of the empty stomach and intestine (23) and therefore possibly linked to the hunger sensation. In fact, icv administration of NPY stimulates food intake and at the same time elicits the fasted pattern of the small intestine (15). CCK and bombesin in the brain are known as feeding-inhibitory peptides, and icv injection of CCK elicits the disruption of fasted motor activities (20, 47). CRF and urocortin are also feeding-inhibitory peptides and cause the disruption of fasted motor activities, as shown in the present study. However, unlike CCK or bombesin, CRF and urocortin are not known to be involved in the regulation of gastrointestinal motility in normal condition (although they may act in stress-induced alteration of gastric and colonic motility (17, 30, 37, 39, 54, 59)), with the exception of the data in isolated rat colon, in which the basal colonic motility was regulated by endogenous CRF (34). This was confirmed by the present results; neither CRF receptor antagonist \(\alpha\)-helical CRF\textsubscript{(9–41)} nor urocortin antiserum administered icv and iv altered the fed and fasted motor patterns of gastroduodenal motility. These results suggest that urocortin originating from the brain and peripheral organs may not be involved in the regulation of basal gastrointestinal motility. It has been reported that urocortin-immunoreactive neurons are widely distributed in the brain nuclei such as the supraoptic nucleus, paraventricular nucleus, substantia nigra, ventral tegmental area, and Edinger-Westphal nucleus (27, 56). Urocortin or urocortin mRNA is also detected in the peripheral sites, including enterochromaffin cells in the intestinal epithelium of the human (24, 25), enteric neurons of the rat (19), and human lymphocytes (3). This central and peripheral urocortin activated by stress or operation may alter gastrointestinal motility.

The present results showed that when urocortin was administered icv or iv in the fed state, the fed motor pattern remained but %MI was decreased in the antrum and increased in the duodenum. The results showed that increase in %MI in the duodenum induced by icv or iv injection of urocortin was a nonpropagated event, since the transit of nonnutrient duodenal contents was decreased by icv or iv injection of urocortin. The inhibitory effect of urocortin on the fed motor activity in the antrum seems consistent with previous reports in which icv and iv injection of CRF or urocortin inhibited gastric emptying (35–37, 41, 43, 53). The duodenal effects were also consistent with the previous reports in which icv infusion of CRF increased the frequency of proximal duodenal contractions and decreased the distally propagating contractions in the whole duodenum of dogs (28) and iv injection of CRF increased the postprandial MI but did not alter the propagated contractions in human duodenum (38). Gastric and duodenal movements seem to be interrelated because gastric emptying causes subsequent duodenal filling and, conversely, duodenal distention elicits reduction in gastric emptying (12, 22). Furthermore, nonpropagated contractions in the duodenum act in the resistance to gastric emptying (18). A vagovagal reflex may play an important role in mediating such feedback control of gastric and duodenal motility (12, 22, 28). Because, however, opposite motor responses of antrum and duodenum occur after vagotomy, the intrinsic myenteric neurons such as nitrergic or nicotinic cholinergic pathways might be involved in this mechanism (42, 55).

To examine the involvement of autonomic nerves in the action of centrally administered urocortin on gastrointestinal motility, the experiments were performed in vagotomized and sympathectomized animals. Results showed that vagotomy abolished the icv urocortin-induced change in the gastroduodenal motility but did not alter the iv urocortin-induced change in the motor activities. Sympathectomy failed to alter the icv and iv urocortin-induced changes in the fed and fasted patterns in both the antrum and duodenum. These data suggest that the effects of icv urocortin on gastrointestinal motility are mediated by vagal nerves.

In summary, the present study examined the effects of icv- and iv-injected urocortin on the physiological fed and fasted motor activity of the antrum and duodenum in freely moving conscious rats. Results showed that both peripherally and centrally administered urocortin disrupted the fasted motor patterns of gastroduodenal motility when administered to animals in the fasted state, whereas urocortin given icv or iv to animals in the fed state caused a decrease in %MI of the antrum and an increase in %MI of the duodenum. The transit was decreased in spite of the increase in the fed motor activity in the duodenum.

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