Gastric Acid Secretion by Central Injection of Dynorphin A-(1 – 17), an Endogenous Ligand of \(\kappa\)-Opioid Receptor, in Urethane-Anesthetized Rats

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ABSTRACT—Gastric acid secretion has been proposed to be regulated by opioid receptors in the central nervous system (CNS). Previously, we reported that central injection of synthetic agonists of \(\kappa\)-opioid receptors stimulated gastric acid secretion in rats, and the secretion by the agonists was inhibited by norbinaltorphimine (an antagonist of \(\kappa\)-opioid receptor). In the present study, we investigated the effect of dynorphin A-(1 – 17), an endogenous ligand of \(\kappa\)-opioid receptor on the gastric acid secretion in the perfused stomach of urethane-anesthetized rats. Injection of dynorphin A-(1 – 17) (0.1 – 1 \(\mu\)g per rat) into the lateral cerebroventricle (LV) stimulated the secretion in a dose-dependent manner. The effect of dynorphin A-(1 – 17) was almost completely inhibited by the LV injection of norbinaltorphimine (10 \(\mu\)g) and in vagotomized rats. Although some studies of dynorphin A-(1 – 17) after central injection showed non-opioid effects such as the involvement of \(N\)-methyl-\(D\)-aspartate (NMDA) receptor, the effect of dynorphin A-(1 – 17) was not inhibited by a selective antagonist of the NMDA receptor ((\(\pm\))-3-(2-carboxypiperazin-4-yl)-1-propylphosphonic acid, 10 \(\mu\)g). The LV injection of naloxone benzoylehydrazone (a \(\kappa\)-opioid receptor agonist, 100 \(\mu\)g) also stimulated the secretion in norbinaltorphimine-sensitive manner. These findings showed that both an endogenous ligand dynorphin A-(1 – 17) and a synthetic \(\kappa\)-opioid receptor agonist stimulated gastric acid secretion via \(\kappa\)-opioid receptors in the CNS of rats in vivo.

Keywords: Gastric acid secretion, Opioid receptor, Dynorphin A-(1 – 17), Central injection

Endogenous opioids and opioid receptors play physiological roles in the peripheral and central nervous system (CNS) (for review, see Refs. 1 – 3). Opioid receptors are divided generally into three types (\(\mu\), \(\delta\) and \(\kappa\)) and each receptor type has distinct roles in the nervous systems (1 – 3). It has been shown that gastric acid secretion is regulated by the opioid system in the CNS (4 – 7), although the effects of morphine (a \(\mu\)-opioid receptor agonist) and \(\kappa\)-opioid receptor agonists are controversial. Fox and Burks (5) reported that the lateral cerebroventricle (LV) injection of proposed \(\kappa\)-opioid receptor agonists including dynorphin A-(1 – 17) did not produce a significant change in gastric acid secretion in rats. However, we recently reported the dual roles of the opioid system in the CNS on gastric acid secretion in rats; an inhibition by morphine with the \(\mu\)-opioid receptor and a stimulation by the agonists of \(\kappa\)-opioid receptor (8). The findings were 1) that the LV injection of synthetic \(\kappa\)-opioid receptor agonists such as U69593 ((5\(\alpha\),7\(\alpha\),8\(\beta\))-(+)-\(N\)-methyl-N-(7-[1-pyrrolidin-1yl]-1-oxaspiro[4.5]dec-8-yl)benzeneacetamide) and bremazocine stimulated the secretion, and 2) that the stimulatory effect of U69593 was inhibited both by naloxone (a non-selective antagonist of opioid receptors) and by norbinaltorphimine (norBNI, a selective antagonist of \(\kappa\)-opioid receptor). However, the effect of dynorphin A-(1 – 17), which is a heptadecapeptide that is an endogenous ligand of the \(\kappa\)-opioid receptor (9, 10), on the secretion has not been established.

Dynorphin A-(1 – 17) has a relatively high binding affinity with \(\kappa\)-opioid receptors in cloned opioid receptors and brain membrane preparations (11 – 14). Recently, however, it was reported that at higher concentrations dynorphin A-(1 – 17) interacts with \(\mu\)- and \(\delta\)-opioid receptors (15, 16) and that dynorphin A-(1 – 17) and its related analogs by central administration show both opioid and non-opioid effects (17, 18). Dynorphin A-(1 – 17) stimulated corticotropin release from a mouse pituitary cell line via non-opioid mechanisms (19). Shukla et al. (20) proposed the involvement of \(N\)-methyl-\(D\)-aspartate (NMDA)
receptor on the central effect of dynorphin A-(1–17) in mice. These findings suggest the non-opioid effects of dynorphin A-(1–17) in neuronal cells and in the CNS. To establish the role of the κ-opioid system in the CNS on gastric acid secretion, the central effect of dynorphin A-(1–17) on the secretion in vivo should be determined.

The aim of the present study was to examine whether 1) central injection of dynorphin A-(1–17) can stimulate gastric acid secretion and 2) the effect is mediated by κ-opioid and/or other receptors in rats. In addition, LV injection of naloxone benzoylhydrazone (NBH, a relatively selective agonist for κ-opioid receptor) was conducted.

MATERIALS AND METHODS

Animals

Male Wistar rats (Takasugi Exp. Animals, Inc., Kusakabe) weighing 210–320 g were used. The animals were housed under controlled environmental conditions (kept at 24 ± 2°C with lights on between 7:00 a.m. and 7:00 p.m.) and fed commercial rat chow (Oriental Yeast Co., Ltd.). The rats were fasted overnight before each experiment with free access to water. Animal experiments were performed in accordance with the Guiding Principles for the Care and Use of Laboratory Animals approved by the Japanese Pharmacological Society.

Drugs

Dynorphin A-(1–17) was purchased from Peptide Institute, Inc. (Osaka). Naloxone hydrochloride, NBH, naloxonazine and norBNI were obtained from Sigma (St. Louis, MO, USA). (±)-3-(2-Carboxypiperazin-4-yl)-1-propylphosphonic acid (CPP) was obtained from Research Biochemicals International (Natick, MA, USA). The doses of the tested drugs by the central injection per rat were as follows: dynorphin A-(1–17) (0.1–1 μg, 46.5–465 pmol), NBH (30 and 100 μg, 67.3 and 224 nmol), norBNI (10 μg, 12.6 nmol) and naloxonazine (10 μg, 13.8 nmol). All compounds were dissolved in 0.9% saline, and the volume for central injections was 5 μl.

Cannulation for central injection

Rats were anesthetized with urethane (1.35 g/kg, i.p.). The rats were placed on a stereotaxic instrument (SR-6; Narishige Scientific Instrument Lab., Tokyo), and a 24 gauge stainless steel guide cannula for microinjection of drugs was implanted into the LV with the following coordinates: 1.0 mm posterior to the bregma, 1.3 mm right lateral to the midsagittal suture, and 3.8 mm vertical to the surface of the skull with the incisor bar set 3.3 mm below the interaural line. For the injection into the third cerebroventricle (3V), the implanting coordinates were as follows: 1.5 mm posterior to the bregma, 0.0 mm lateral and 4.5 mm vertical from the surface of the skull. For the injection into the fourth cerebroventricle (4V), the implanting coordinates were 11.5-mm posterior to the bregma, 0.0-mm lateral and 7.5-mm vertical from the surface of the skull. The cannula was secured with dental cement. At the end of the experiments, Evans blue solution was injected to confirm that the solution had diffused into each cerebral cavity.

Experimental procedures and measurement of gastric acid secretion

After the cannulation for injections, the animals were operated on for the measurement of gastric acid secretion. The rats were used for the measurement of secretion one hour after the implantation of cannulas and the bilateral vagotomy at cervical level. After the determination of basal acid secretion for 30 min, each test compound was injected. Opioid receptor antagonists were administrated 10 min before the injection of opioid receptor agonists. Gastric acid secretion was determined by gastric perfusion methods as described previously (4, 21, 22) with minor modifications (8). The trachea was exposed, then cannulated and the esophagus was ligated at the cervical level. After laparotomy, the pylorus was ligated and a dual cannula was inserted into the gastric lumen from the forestomach. The stomach lumen was continuously perfused with saline (adjusted to pH 5.0 with 0.1 N HCl, at 37°C) through the inlet tube of the dual cannula connected to the perfusion pump at the rate of 1 ml/min. The stomach was maintained at a pressure of 5 cm H2O. After 30 min of pre-perfusion, the perfusate flowing from the outlet tube was collected as 10 min fractions with a fraction collector and titrated to pH 5.0 with 0.02 N NaOH using an autonomic titrator (AUT-201; Toa Electronics Ltd., Tokyo). In our conditions, titration to pH 5.0 was used in order to avoid the buffering action of gastric mucus (4, 8, 21, 22). The acid output was expressed in terms of μEq HCl/10 min.

Statistical analyses

The values are expressed as means ± S.E.M. of 4–6 rats. The statistical differences between two groups were assessed with Student’s t-test followed by the F-test. P<0.05 was considered statistically significant.

RESULTS

Stimulatory effect of dynorphin A-(1–17), an endogenous ligand of κ-opioid receptors, on gastric acid secretion

First, we investigated the effect of dynorphin A-(1–17) on the gastric acid secretion from urethane-anesthetized rats. The LV injection of dynorphin A-(1–17) increased gastric acid secretion in a dose-dependent manner (Fig. 1A). The secretion began to increase about 10 min
after the injection, and increased until the peak level at 40 – 50 min, similar to the secretion stimulated by synthetic \( \kappa \)-opioid receptor agonists (8). The LV injection of dynorphin A-(1 – 17) at a low dose, 0.1 \( \mu \)g per rat, significantly stimulated the total secretion in the period of 0 – 60 min (Fig. 1B). The LV injection of dynorphin A-(1 – 17) at higher doses (0.3 and 1 \( \mu \)g) also stimulated the secretion markedly. The secretion stimulated by dynorphin A-(1 – 17) (0.3 \( \mu \)g) returned to the basal level at 120 min after the injection, and the 2nd injection of the same dose of 

dynorphin A-(1 – 17) into the LV also stimulated the secretion in a similar pattern to that by the 1st injection (Fig. 2). The total acid output for 120 min by the 2nd LV injection of dynorphin A-(1 – 17) (0.3 \( \mu \)g) was 87.1 ± 44.1 \( \mu \)Eq HCl (n = 4), which was similar to the value (100.9 ± 25.0, n = 4) at the 1st injection.

Histamine is released from enterochromaffin-like cells in the fundic gland and one of major stimulators of gastric acid secretion. In our conditions, the total acid output for 120 min by the LV injection of dynorphin A-(1 – 17) (1 \( \mu \)g) was 175.8 ± 34.1 \( \mu \)Eq HCl (n = 4), which was almost same as the value (209.1 ± 6.3, n = 4) in the histamine-treated group (20 mg/kg, s.c.). Intravenous injection of 0.3 \( \mu \)g/rat of dynorphin A-(1 – 17) did not stimulate the secretion (data not shown). The gastric acid secretion stimulated by the LV injection of dynorphin A-(1 – 17) was completely inhibited by the bilateral vagotomy at cervical level; the total acid secretion for 120 min by dynorphin A-(1 – 17) (1 \( \mu \)g) in the sham-operated rats and the vagotomy-treated rats were 175.8 ± 34.1 and 6.2 ± 3.7 \( \mu \)Eq HCl (n = 5, \( P < 0.001 \)), respectively.

Previously, we showed that LV injection of synthetic \( \kappa \)-opioid receptor agonists stimulated gastric acid secretion at lower doses compared with the 4V injection (8). In the present study, the 4V injection of dynorphin A-(1 – 17) (0.1 and 0.3 \( \mu \)g) showed no effect, and 1 \( \mu \)g of dynorphin A-(1 – 17) stimulated the secretion slightly (Fig. 3). Injection of 3 \( \mu \)g of dynorphin A-(1 – 17) stimulated the secretion significantly: the total acid secretion in the period of 0 – 60 min in the 3 \( \mu \)g of dynorphin A-(1 – 17)-treated and
the amount of gastric acid output for 10 min and is the mean ± S.E.M. of 4 rats.

Inhibition of dynorphin A-(1–17)-stimulated gastric acid secretion by opioid receptor antagonists, but not by NMDA-receptor antagonist

As mentioned in the Introduction, the characterization of effects induced by dynorphin A-(1–17) is controversial and includes opioid and non-opioid components of actions (17–20). We investigated the effect of norBNI, a selective κ-opioid receptor antagonist (23), on the gastric acid secretion stimulated by dynorphin A-(1–17) (Fig. 3). The LV injection of norBNI (10 μg) completely inhibited the secretion stimulated by the LV injection of dynorphin A-(1–17).

Next, we investigated the effect of LV injection of CPP (10 μg), a selective antagonist of the NMDA receptor, on gastric acid secretion stimulated by dynorphin A-(1–17). The total acid secretion in the period of 0–120 min by LV injection of dynorphin A-(1–17) (1 μg) was slightly but not significantly (P = 0.08) inhibited by the LV injection of CPP; the values were 83.6 ± 25.4 (n = 4) and 175.8 ± 34.1 μEq HCl (n = 5) in the CPP-treated and the control groups, respectively. The total acid secretion in the period of 0–60 min by LV injection of dynorphin A-(1–17) in the CPP-treated rats was 67.0 ± 26.1, which was similar to that in the control rats without CPP, 102.0 ± 23.1 μEq HCl. Interestingly, the total secretion in the period of 60–120 min in the CPP-treated rats was 16.6 ± 2.4 μEq HCl, which was significantly (P < 0.01) smaller than that in the control rats (73.8 ± 13.8). These findings suggest that the LV injection of dynorphin A-(1–17) stimulated gastric acid secretion without the involvement of NMDA receptors at least during the initial stage (0–60 min) in rats.

Effect of NBH, a κ-opioid agonist, on gastric acid secretion

Dynorphin A-(1–17) reacts with κ1-, κ2- and κ3-opioid receptors with similar affinity (1–3, 9). In the present study, we investigated the effect of NBH, a relatively selective agonist of κ3-opioid receptor (24, 25), on gastric acid secretion. The LV injection of NBH (30 and 100 μg) stimulated gastric acid secretion (Fig. 5A). The effect of NBH (100 μg) was completely inhibited by the LV injection of norBNI (10 μg) (Fig. 5B). These findings suggest that activation of κ3-opioid receptors in the CNS stimulates gastric acid secretion in rats.
DISCUSSION

\(\kappa\)-Opioid receptor-mediated gastric acid secretion by dynorphin A-(1–17)

In the present study, we showed that microinjection of dynorphin A-(1–17) into the LV and/or the 3V of the CNS stimulated gastric acid secretion in rats. Recent studies suggested that dynorphin A-(1–17) displayed both opioid and non-opioid effects in different species in vivo. For example, i.c.v. injection of dynorphin A-(1–17) caused severe motor dysfunction in mice, and this impairment was not reversed by naloxone but was significantly blocked by NMDA-receptor antagonists such as CPP (17, 20). Intravenous administration of dynorphin A-(1–17) decreased food-reinforced responses in monkeys, and the inhibitory effect of dynorphin A-(1–17) was not reversed by quadi-zocine (an opioid receptor antagonist) (18). Cheng et al. (19) reported that dynorphin A-(1–17) stimulated the release of corticotropin but the effect was not mediated by \(\kappa\)-opioid receptors or by NMDA receptors in the mouse anterior pituitary AtT-20 cells. Thus, central or systemic administration of dynorphin A-(1–17) appears to have complex effects in vivo. In the present study, however, gastric acid secretion stimulated by the LV injection of dynorphin A-(1–17) in rats was completely inhibited by norBNI, a \(\kappa\)-opioid receptor antagonist. In addition, the gastric acid secretion stimulated by dynorphin A-(1–17) in the period of 0–60 min was not inhibited by the LV injection of CPP, an antagonist of NMDA receptor. The effect of dynorphin A-(1–17) was completely inhibited in vagotomy-treated rats. These findings show that the effect of centrally injected dynorphin A-(1–17) on the gastric acid secretion was mediated by opioid receptors in the CNS of rats. Further studies are necessary to show the possible involvement of NMDA receptors on dynorphin A-(1–17)-stimulated gastric acid secretion in the later phase (in the period of 60–120 min after the stimulation).

Dynorphin A-(1–17) is an endogenous ligand to opioid receptors. Although dynorphin A-(1–17) has high affinity to \(\kappa\)-opioid receptors (11–14, 26), dynorphin A-(1–17) at higher concentrations interacts with \(\mu\)- and \(\delta\)-opioid receptors in vitro (15, 16). Clark et al. (27, 28) showed that dynorphin A-(1–17) reacts with \(\delta\)-opioid receptors, specifically \(\delta_1\)-opioid receptor with high affinity by receptor binding experiments. Previously, we reported that the i.v. infusion (4) and the 4V injection (8) of morphine, which prefers \(\delta\)-opioid receptor, inhibited 2-deoxy-D-glucose-stimulated gastric acid secretion in rats. Morphine alone had no effect on the basal secretion. Since the inhibitory effect of morphine by the 4V injection was more potent than that by the LV injection, morphine appeared to inhibit the secretion by \(\delta\)-opioid receptors in the 4V (8). Synthetic \(\delta\)-opioid receptor agonist did not show either stimulatory or inhibitory effects on the gastric acid secretion (8). In the present study, injection of low doses (0.3 and 1 \(\mu\)g) of dynorphin A-(1–17) to the LV, but not to the 4V, stimulated gastric acid secretion markedly. The 4V injection of dynorphin A-(1–17) (1 \(\mu\)g) did not inhibit the 2-deoxy-D-glucose-stimulated gastric acid secretion in rats (data not shown). In addition, the effect of dynorphin A-(1–17) was inhibited by norBNI, a \(\kappa\)-opioid receptor antagonist. The gastric acid secretion stimulated by the activation of \(\kappa\)-opioid receptor with dynorphin A-(1–17) was not observed in vagotomized rats, which was similar to the secretion observed using synthetic \(\kappa\)-opioid agonist U69593 (8). These findings suggest that dynorphin A-(1–17)
physiological systems (29, 30). Previously, we reported that to be mediated by activation of 25). However, the stimulatory effect of NBH appeared of feeding after central administration, and the LV injection by acoustic stress in dogs. Dynorphin A potently stimulated U50488H blocked the inhibition of gastric motility induced receptor agonists including dynorphin A-(1–13), a selective μ-opioid receptor antagonist (31), did not stimulate gastric acid secretion (data not shown). Thus, κ1-, κ2- and κ3-opioid receptors in the CNS all appeared to be involved in stimulation of gastric acid secretion in rats. However, there are difficulties in clarifying the exact role of each type of κ-opioid receptor. The further development of type-selective agonists and antagonists of κ-opioid receptors and/or molecular biological techniques such as type-selective κ-opioid receptor knockout mice would help to clarify the character of κ-opioid receptor types on gastric acid secretion.

Possible physiological role of the κ-opioid system on gastric functions

Gue et al. (32) reported that the LV injection of κ-opioid receptor agonists including dynorphin A-(1–13) and U50488H blocked the inhibition of gastric motility induced by acoustic stress in dogs. Dynorphin A potently stimulated feeding after central administration, and the LV injection of [D-Ala²]dynorphin A-(1–13), a more stable analog of dynorphin A, could override the decrease in food intake by gastric satiety factors such as rumen distension in sheep (33). In the present study, microinjection of dynorphin A-(1–17) into the LV and 3V stimulated gastric acid secretion markedly. The 3V injection of 0.1 μg of dynorphin A-(1–17) tended to stimulate the secretion faster and more effectively compared with the LV injection, but the injection of the same dose to the 4V did not stimulate secretion. These previous and the present findings suggest the involvement of the κ-opioid system located in the LV region and/or hypothalamus in gastric functions. Dynorphins including dynorphin A-(1–17) are endogenously produced in the CNS including the hypothalamus and the contents are variable in several conditions in vivo (34, 35). Some changes in gastrointestinal motility or gastric emptying are reduced by the ventral infusion of naloxone in humans (36, 37). The contribution of endogenous dynorphins on the regulation of gastric acid secretion should be determined in future studies.

In conclusion, not only synthetic κ-opioid receptor agonists but also an endogenous ligand dynorphin A-(1–17) by LV injection stimulated gastric acid secretion via κ-opioid receptors in the CNS of rats. In addition, the LV injection of κ3-opioid receptor agonist also stimulated the secretion. It was suggested that these findings establish the positive regulation of gastric acid secretion in rats by the κ-opioid system in the CNS via a vagal mechanism.

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