Effect of Anterior Unilateral Vagotomy on Healing of Kissing Gastric Ulcers Induced in Rats

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ABSTRACT—Unilateral vagotomy causes atrophy of the denervated fundic mucosa in rat stomachs. We examined whether or not unilateral vagotomy delays healing of gastric ulcers induced on the denervated mucosa. Kissing ulcers were induced in the fundus of rat stomachs by intraluminal application of an acetic acid solution. Anterior unilateral vagotomy was performed subdiaphragmatically at the time of ulceration. The healing of gastric ulcers induced on the denervated side was significantly enhanced, whereas that on the vagally intact side was not affected. In unilaterally denervated animals, the total gastric acid secretion (both basal and 2-deoxy-D-glucose stimulated) was inhibited, and the pH around the ulcers was increased only in the anterior side. Repeatedly administered histamine failed to affect the enhanced ulcer healing in unilaterally denervated animals. Gastric emptying and mucosal cell proliferation stimulated by food or pentagastrin were unaffected. Serum gastrin significantly increased 19 days after vagotomy. Gastric relaxation on refeeding was inhibited on the denervated side, but this inhibition of relaxation was reversed by hexamethonium treatment. A liquid diet significantly enhanced the healing of ulcers on both the denervated and vagally intact sides. The mechanism by which unilateral vagotomy accelerates the healing of ulcers on the denervated side appears to relate to the inhibition of both gastric acid secretion and gastric relaxation.

Keywords: Kissing gastric ulcer, Anterior unilateral vagotomy, Ulcer healing, Cell proliferation, Gastric relaxation

Håkanson et al. (1) reported that unilateral vagotomy resulted in atrophy of the fundic mucosa (the oxyntic gland area) on the denervated side of rat stomachs, as reflected by significant reductions in the mucosal height and weight, and the number and density of enterochromaffin-like cells. In addition, they found that hyperplasia of the fundic mucosa due to prolonged treatment with omeprazole was less marked on the unilaterally denervated side compared with that on the vagally intact side (2). Kiba et al. (3) recently reported that ventromedial hypothalamic lesions increased DNA synthesis in the gastrointestinal mucosa, most probably through the trophic control of the vagus over this tissue. These results strongly suggest that the vagus plays an important role in maintenance of the mucosal integrity by regulating cell proliferation. Therefore, it is postulated that unilateral vagotomy delays the healing of gastric ulcers induced in the denervated fundic mucosa. We herein examined the effect of unilateral vagotomy on the healing of experimental gastric ulcers. For that purpose, we used the kissing ulcer model, consisting of one ulcer on the anterior side and another one on the posterior side of the same size (4). Unexpectedly, the healing of gastric ulcers was significantly enhanced after unilateral vagotomy, so the underlying mechanism was determined.

MATERIALS AND METHODS

Animals

Male Donryu rats (Charles-River Japan, Atsugi), weighing 240–260 g, were used in all experiments. They were kept in mesh-bottom cages and had free access to a standard chow (CE-2; Nihon Clea, Osaka) and tap water. Under ether anesthesia, the anterior vagal trunk was sectioned just below the diaphragm, leaving the posterior trunk intact (anterior unilateral vagotomy; AUV). Animals were deprived of food for 24 hr before the experiments, unless otherwise mentioned. Drinking water was freely available to the animals up to 2 hr before the experiments. During fasting, all animals were kept in raised mesh-bottom cages to prevent coprophagy. Each group consisted of 5–10 rats.
**Induction of kissing gastric ulcers**

Under ether anesthesia, the abdomen was incised and the stomach exposed. Both the anterior and posterior walls of the gastric fundus were clamped together with forceps with a round ring (ID, 9 mm) (Fig. 1). A 60% (v/v) acetic acid solution (0.2 ml) was injected into the clamped lumen with a needle (gauge 21) through the forestomach. Forty-five seconds later, the acid was removed and the abdomen closed. The animals were fed normally thereafter. AUV was performed at the time of ulcer production in the following study. To determine the sizes of the ulcers, the stomach of each animal, which had been fasted for 24 hr prior to autopsy, was removed. These stomachs were inflated by injecting 8 ml of 2% formalin and then immersed in 2% formalin for 15 min. This procedure allows light fixation of the gastric wall for easier examination of ulcers. Each stomach was then opened along its greater curvature, and the areas (mm²) of the ulcers were determined under a dissecting microscope (× 10; Olympus, Tokyo) with a square grid. The person (SO) who determined the ulcer sizes did not know the treatment given to the animals.

**Determination of gastric acid secretion**

Basal and 2-deoxy-d-glucose (2-DG; Wako Chemicals, Osaka) stimulated gastric secretion was determined by means of a pylorus ligation in animals with or without ulcers. In animals without ulcers, AUV was performed immediately before the ligation. In animals with ulcers, AUV was performed at the time of ulceration. The pylorus was ligated under ether anesthesia through a short midline incision. For basal secretion, the animals were killed 3 hr later, and the gastric contents were collected and analyzed for volume and acidity. The acidity was determined by automatic titration of the contents against 0.1 M NaOH to pH 7.0 (Comitie 5; Hiranuma, Tokyo). Total acid output (volume × acidity) was expressed as μEq/hr. For stimulated secretion, 2-DG was injected intravenously at the dose of 200 mg/kg immediately after the ligation (5). Two hours after the ligation, the animals were killed, and the gastric contents were collected and analyzed.

**Determination of mucosal pH**

Non-fasted animals with 5-day-old ulcers with or without AUV were killed at 12:00 a.m. and 12:00 p.m. The stomach was removed and opened along the greater curvature and inflated on a cork board. After removing the gastric contents, mucosal pH around the gastric ulcers in the anterior and posterior sides was measured, using a pH test paper (Advantec, Tokyo).

**Effect of histamine on ulcer healing**

Histamine 2HCl (Nacalai Tesque, Kyoto), dissolved in saline, was administered subcutaneously at 20 mg/kg 3 times a day to animals with AUV for 2 weeks from 5 days after ulceration. Control animals received vehicle alone.

**Histological analysis**

Small pieces of the stomach containing ulcers in animals with 19-day-old ulcers were fixed with 10% formalin, and processed for routine light microscopy, sectioned at 4 μm, and stained with hematoxylin and eosin.

**Determination of cell proliferative activity**

The cell proliferative response of the fundic mucosa in

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**Fig. 1.** Schematic illustration of induction of kissing gastric ulcers in a rat. An acetic acid solution (60%, 0.2 ml) was topically applied to the fundic portion clamped with forceps with a ring. The injected portion swelled without leakage of the solution.
animals with or without AUV was determined by measuring the incorporation of \(^{3}\text{H}\)-thymidine into DNA after pentagastrin (Sigma, St. Louis, MO, USA) administration or refeeding (6). AUV was performed 19 days before the experiments. In the case of pentagastrin treatment, the animals, fasted for 24 hr, were killed 16 hr after intraperitoneal administration of the agent (250 \(\mu\)g/kg). Pentagastrin was dissolved in a small amount of ammonium hydroxide and diluted with saline. In the case of refeeding, the animals were fasted for 48 hr and killed 20 hr after refeeding. The fundic mucosae on the anterior and posterior sides were scraped with a glass slide. These mucosae were incubated for 30 min at 37\(^{\circ}\)C in medium 199 (Wako Chemicals) containing 2 \(\mu\)Ci/ml of \(^{3}\text{H}\)-thymidine (specific activity, 10 Ci/mmol; American Radiolabeled Chemicals, St. Louis, MO, USA). The reaction was stopped with perchloric acid and the mucosae hydrolyzed with KOH to remove RNA. DNA was dissolved in 100\% perchloric acid and then centrifuged to remove denatured protein. The incorporation of \(^{3}\text{H}\)-thymidine into DNA was determined by counting 1.0 ml of the DNA-containing supernatant with a scintillation counting system (TRICARB 2000 CA; Packard, Zurich, Switzerland). The DNA content of samples was determined with calf thymus DNA as the standard (7, 8). DNA synthesis was expressed as disintegrations per minute per microgram of DNA.

**Determination of serum gastrin**

Under ether anesthesia of non-fasted animals with 12- or 19-day-old ulcers, blood samples of about 5 ml were collected in centrifugation tubes. The samples were left for 1 hr, and then they were centrifuged for 20 min at 3,500 rpm. The serum was stored frozen until analysis. Gastrin concentrations were determined by double-antibody, \(^{125}\text{I}\)-radioimmunoassay (Sanyoh-Kasei, Tokyo). Results were expressed as pg per ml of serum. The ulcerated area was not determined in this experiment because the stomach was full of ingested food which hindered the injection of formalin solution.

**Determination of gastric emptying**

Animals with 5- or 19-day-old ulcers were deprived of food (but not water) for 48 hr before the experiments and then refed freely for 1 hr. They were killed 0, 2, 4 and 6 hr after refeeding and then the gastric contents collected. These contents were centrifuged at 600 rpm for 5 min and the total volume (ml) determined.

**Determination of gastric relaxation**

Animals with or without ulcers were deprived of food for 48 hr and refed for 2 hr. Subsequently, the animals were killed and their stomachs removed. To fix the outer layer, the stomachs were immediately immersed in 10\% formalin for 15 min. The stomachs were then opened along their greater curvature, and the areas of the fundic mucosa on the anterior and posterior sides were measured with a planimeter (X-PLAN360; Ushitaka, Tokyo). The results are expressed as the raw data or the % changes from the data of fasted animals. Hexamethonium (Wako Chemicals) was administered at 10 mg/kg, s.c. at 30 min before the refeeding of animals with or without AUV. The dose used was that used by Niida et al. (9) and Flemström et al. (10) to block ganglionic transmission.

**Effect of a liquid diet on ulcer healing**

The animals were given a liquid diet (Elental; Ajinomoto, Tokyo) instead of the usual rat chow, using a drinking bottle, for 2 weeks from 5 days after induction of kissing ulcers in AUV rats. The liquid diet consisted of amino acids such as L-glutamine, L-serine, L-leucine, Lysine HCl, etc.; carbohydrate; lipids; minerals and vitamins. The diet ingested in one day contained about 60 kcal, which is nearly equal to the value for the chow used.

**Analysis of data**

All data are presented as means±S.E.M. Statistical analyses were performed by the two-tailed Dunnett's multiple comparison test, and values of \(P<0.05\) were regarded as significant.

**RESULTS**

**Healing of kissing gastric ulcers**

Ten minutes after intraluminal application of an acetic acid solution, both the anterior and posterior sides exhibited clearly defined superficial necrosis of the fundic mucosa to nearly the same extent. The severity of the damage gradually increased with time and penetrating ulcers occurred 5 days after injection in all animals, just as kissing ulcers (Fig. 2). The ulcerated areas were 31.1 \(\pm\) 1.8 mm\(^2\) and 30.2 \(\pm\) 1.3 mm\(^2\) (n=10) on the anterior and posterior sides, respectively. There was no adhesion of the ulcer base to the surrounding organs. At this point, this ulcer model shows a great resemblance to human peptic ulcers, in contrast to thermal or acetic acid ulcers, which exhibit severe adhesion. Histologically, these ulcers extended through the muscularis mucosa into the submucosa or deeper, and the severity was much the same on both sides. These ulcers healed with time at a similar rate; the ulcerated areas were 8.1 \(\pm\) 0.7 mm\(^2\) and 8.6 \(\pm\) 0.8 mm\(^2\) (n=10) on the anterior and posterior sides, respectively, 19 days after ulceration (Fig. 3). Even 33 days later, however, there were still small and shallow ulcers on both sides.
Fig. 2. Gross appearance of kissing gastric ulcers induced in the fundic mucosa of a rat 5 days after application of the acetic acid solution. Note that the ulcers induced on both sides are nearly the same in size and severity.

Effect of AUV on ulcer healing

Five days after the acid application, the ulcerated areas in animals with AUV were 28.9 ± 1.9 mm² and 29.8 ± 2.1 mm² (n=10) on the anterior and posterior sides, respectively. Twelve and nineteen days later, there was significant enhancement of ulcer healing on the denervated side; i.e., the ulcerated areas were 5.9 ± 0.5 mm² and 2.3 ± 0.2 mm² on the anterior side and 11.8 ± 1.0 mm² and 8.8 ± 1.5 mm² (n=10) on the posterior side, respectively (Fig. 3). Similar changes were observed even 33 days later (0.8 ± 0.4 mm² on the anterior side vs. 2.9 ± 0.8 mm² on the posterior sides, n=10). There were no changes in dai-

![Graph showing healing of kissing gastric ulcers](image-url)

Fig. 3. Healing of kissing gastric ulcers in vagally intact and anterior unilateral vagotomized (AUV) rats. The animals were killed at 5, 12, 19 and 33 days after ulceration. ■, vagally intact; □, AUV. A, anterior side; P, posterior side. Data are means ± 1 S.E.M. from 10 animals. *Significant difference between the anterior and posterior sides, at P<0.05.
ly ingestion of food and water or weight gain in AUV animals. Histologically, both the size of the ulcer and the length of ruptured muscularis mucosa were much smaller in the denervated side when compared to the vagally intact side (Fig. 4).

**Effects of AUV on basal and 2-DG stimulated gastric acid secretion**

In animals without ulcers, the basal gastric secretion was $4.6 \pm 1.0$ ml/rat and $133.0 \pm 19.3$ µEq/hr in the vagally intact group vs. $3.2 \pm 1.0$ ml/rat and $62.2 \pm 9.8$ µEq/hr ($n=8$) in the AUV group (Fig. 5). These differences were statistically significant. The same tendency as to basal secretion was observed in animals with 19-day-old ulcers, although the reduction of acid output was not significant. 2-DG significantly stimulated gastric acid secretion in animals with or without ulcers compared with the vehicle-treated animals. The stimulation of acid output in animals without ulcers was evident; i.e., $216.9 \pm 27.1$ µEq/hr vs. $60.8 \pm 24.2$ µEq/hr ($n=8$) in the vehicle-treated animals. AUV caused a significant reduction by 50% in 2-DG-stimulated gastric secretion. In the animals with 19-day-old ulcers, the increase in 2-DG-stimulated acid secretion was less marked than that in the animals without ulcers. AUV caused a significant reduction by 40% in the stimulated gastric secretion.

**Effect on mucosal pH**

The data on the mucosal pH are summarized in Table 1. At 12:00 a.m., there was no significant difference be-

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**Fig. 4.** Histological appearance of 19-day-old kissing gastric ulcers in the rats with AUV. A, anterior; P, posterior. (×6.3).
tween the anterior and posterior sides in vagally intact animals. However, the pH of the anterior side was significantly higher than that of the posterior side in AUV animals. Nearly the same results were obtained at 12:00 p.m. At these times, gastric contents were less and had a gruel-like appearance.

**Effects of histamine on ulcer healing**

Histamine administered for 2 weeks significantly increased gastric secretion; the gastric acid output was 270.4 ± 17.2 μEq/hr vs. 123.7 ± 11.1 μEq/hr (n = 8) in the vehicle-treated animals. However, repeated administration of histamine had no effect on the spontaneous healing of kissing ulcers or on the enhanced healing caused by AUV; the ulcerated areas were 4.3 ± 1.0 mm² on the anterior side and 10.6 ± 1.2 mm² (n = 8) on the posterior side.

**Effect of AUV on the trophic response to pentagastrin and refeeding**

Pentagastrin significantly increased about 2-fold the incorporation of ³H-thymidine into DNA on both sides of the fundic mucosa in vagally intact and AUV animals (Fig. 6). There was no significant difference between the anterior and posterior sides. In contrast, ³H-thymidine incorporation in response to refeeding increased to 7- to 8-fold in the fundic mucosa on both sides in vagally intact or AUV animals. Again, there was no significant difference between the two sides.

**Effect of AUV on serum gastrin**

Twelve days after ulceration, serum gastrin levels in vagally intact and AUV animals were 472.3 ± 42.6 pg/ml and 524.8 ± 35.9 pg/ml (n = 8), respectively (no significant difference). Nineteen days later, however, the gastrin level in AUV animals was significantly higher than that in intact ones (568.1 ± 41.1 pg/ml vs. 452.3 ± 34.7 pg/ml, n = 8).

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**Table 1. Effect of AUV on mucosal pH in rats**

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Mucosal pH in the animals with 5-day-old ulcers was measured at 12:00 a.m. and 12:00 p.m. Data are means ± S.E.M. from 4-6 animals. *Significant difference between the anterior and posterior sides, at P < 0.05.
Fig. 6. Effect of AUV on pentagastrin and refeeding stimulated cell proliferation in the gastric fundus of rats. Pentagastrin (250 µg/kg) was administered intraperitoneally after 24-hr fasting. The animals were killed 16 hr later, and ³H-thymidine incorporation into DNA of the fundic mucosa was determined. Refeeding was performed after 48-hr fasting, and ³H-thymidine incorporation was determined 20 hr after refeeding. ■, Vagally intact; ◊, AUV. A, anterior; P, posterior. Data are means±1 S.E.M. from 5–7 animals. *Significant difference from the corresponding vehicle or fasting groups, at P<0.05.

Effect of AUV on gastric emptying

In animals with 5-day-old ulcers, the gastric contents were 4.2±0.7 ml in vagally intact animals and 4.1±0.8 ml in AUV animals (n=8) immediately after refeeding (no significant difference). These gastric contents were quickly emptied within 2 hr and became almost zero at 4 and 6 hr later, respectively. In animals with 19-day-old ulcers, the gastric contents were apparently increased compared with those in animals with ulcers on Day 5; i.e., 7.1±0.5 ml in vagally intact animals and 6.5±0.6 ml (n=8) in AUV animals (no significant difference). The contents in both groups then gradually decreased with time in a similar manner, except for the significantly smaller contents in AUV animals at 4 hr.

Fig. 7. Effect of AUV on gastric distension induced by refeeding in rats with or without ulcers. The animals were fasted for 48 hr, refeed for 2 hr and then killed to determine the area of the fundic mucosa. ■, Vagally intact; ◊, AUV. A, anterior; P, posterior. Data are means±1 S.E.M. from 8–10 animals. *Significant difference from the corresponding fasting groups, at P<0.05. ◊Significant difference between the anterior and posterior sides, at P<0.05.

Effect of AUV on gastric relaxation

The fundic areas in vagally intact animals after 48 hr fasting were 2.3±0.1 cm² on the anterior side and 2.5±0.1 cm² (n=10) on the posterior side. After 2 hr refeeding, these areas had significantly increased to 3.8±0.1 cm² (151.1%) on the anterior side and 4.0±0.1 cm² (159.9%) (n=10) on the posterior side compared with those in the case of fasting alone (Fig. 7). Hexamethonium treatment had no appreciable effect on gastric relaxation. In AUV animals, the fundic areas after fasting were 2.1±0.1 cm² and 2.6±0.1 cm² (n=8) on the anterior and posterior sides, respectively. The area on the posterior side was thus significantly larger than that on the anterior side. After refeeding, these areas increased to 2.6±0.1 cm² (123.2%) and 4.2±0.2 cm² (162.9%) (n=8) on the anterior and posterior sides, respectively. Hexamethonium treatment in AUV animals abolished the effect of vagal denervation on gastric distension (Fig. 8). Nearly the same results were obtained for animals with
Effect of a liquid diet on ulcer healing

In AUV animals fed with the normal chow, the healing of ulcers on the anterior side was significantly enhanced in contrast to that on the posterior side. With a liquid diet, however, the ulcers on both sides healed 19 days later; the ulcerated areas were 0.3 ± 0.1 mm² and 1.7 ± 0.3 mm² (n = 8) on the anterior and posterior sides, respectively. The difference between the anterior and posterior sides was statistically significant.

DISCUSSION

These results confirmed that the kissing gastric ulcer model is a useful one for investigating the healing mechanism of gastric ulcers because of the simplicity of induction, the similar healing processes of the two ulcers, and lack of adhesion to the surrounding organs. In particular, this model was found to be quite valid for elucidation of the effect of AUV on ulcer healing and the underlying mechanism. It is known that one vagal nerve innervates only one side of the glandular mucosa, having no effect on the opposite side (1). This indicates that ulcers induced on the innervated side might serve as an appropriate control for ulcers on the denervated side.

Using this ulcer model, we found that AUV significantly enhanced the healing of ulcers induced on the denervated side of the stomach 12, 19 or 33 days later. This enhanced ulcer healing caused by AUV is consistent with the clinical finding that highly selective vagotomy enhances ulcer healing, which is usually resistant to medical treatment (11).

The question of why AUV enhances the healing of ulcers on the denervated side could be raised. The following considerations will provide an answer. First, does the reduced gastric acid secretion caused by AUV contribute to the enhanced healing? Indeed, we confirmed that basal and 2-DG-stimulated gastric secretions in animals without ulcers were significantly inhibited by AUV, maximally by > 50%. Although these secretions in animals with ulcers were also inhibited, the degrees of inhibition were less marked than those in animals without ulcers. The reason for the reduced response to AUV in animals with ulcers remains unknown. A possible explanation is that the number of parietal cells decreased in animals with kissing gastric ulcers, because these ulcers were induced in the oxyntic glandular area. Since both the anterior and posterior ulcers develop in the identical stomach, the acidic condition is thought to be almost the same on both sides. Repeated administration of histamine induces hypersecretion of acid and delays the healing of conventional acetic acid ulcers (12, 13). However, it failed to affect the enhanced ulcer healing caused by AUV. Therefore, it is questionable that reduced gastric acid secretion is extensively associated with enhanced ulcer healing by AUV. As expected from the data of Håkanson et al. (1), the mucosal pH (about 1.7–2.0) of the anterior side was significantly higher than that of the posterior side (about 1.4) in AUV animals when examined at 12-hr interval. Accordingly, the local inhibition of acid secretion may partly contribute to the enhanced ulcer healing caused
by AUV.

There have been some reports suggesting that epithelial cell proliferation plays an important role in ulcer healing (14-16). As described already, Håkanson et al. (1, 2) and Kiba et al. (3) found that the vagus exerts trophic control over the fundic mucosa to maintain the mucosal integrity. It should be noted that the mucosa they used was intact, i.e., no ulcers were present. Despite their observation, we found that AUV significantly enhanced the healing of ulcers on the denervated side of the stomach. To clarify the role of the vagus in cell proliferation, we examined the effect of AUV on mucosal cell proliferation stimulated by pentagastrin and refeeding in animals without ulcers. We could not find any significant difference in mucosal DNA synthesis between the vagally intact and denervated sides. Therefore, it is unlikely that the increased cell proliferation is involved in the mechanism of enhanced healing caused by AUV. It was reported that the gastric mucosa resected from the ulcer margin, including the granulation tissue, showed significantly higher DNA synthesis and higher DNA and RNA concentrations (16). Determination of whether or not cell proliferation and DNA synthesis at the ulcer edge is affected by AUV is our ongoing subject of investigation. In the present study, we found that there was either insignificant or significant increase in serum gastrin levels between vagally intact and AUV animals with 12- or 19-day-old ulcers, respectively. It seems unlikely that circulating gastrin would affect the ulcer healing because the 12-day-old ulcers were enhanced to heal without a significant increase of serum gastrin. In addition, the increased gastrin level observed 19 days after ulceration would not contribute to the enhanced ulcer healing because there was no enhanced proliferation of the gastric mucosa.

Bilateral vagotomy is reportedly known to delay gastric emptying and ulcer healing, most probably due to the prolonged distension time (17, 18). The present study showed that gastric emptying was almost the same in the vagally intact and AUV groups, thereby indicating that one vagal nerve is sufficient for normal gastric emptying. These results indicate that the gastric emptying factor is also not involved in the enhanced ulcer healing caused by AUV.

Of interest is that we invariably found that the stomachs of AUV animals had a strange shape; the anterior side was small and the posterior side large compared with the stomachs in vagally intact animals. It is known that the stomach relaxes in response to feeding via a vagus-dependent mechanism, and this mechanism is called gastric or receptive relaxation (19). Thus, it is possible that the anterior side in AUV animals could not relax, resulting in the smaller size compared to the innervated posterior side. Although the methods used for making the determination of inhibited gastric relaxation were crude, the gastric relaxation in AUV animals was found to be inhibited only on the anterior side. Hexamethonium is known to block intramural ganglia so as to block stimulatory and inhibitory neurons. In the present study, we found that hexamethonium pretreatment before refeeding was less effective on gastric distension in vagally intact animals and that the inhibition of gastric distension caused by AUV was not observed in hexamethonium treated animals. It is thought that the stomach was distended by the physical force of food intake in hexamethonium treated animals. Therefore, it is suggested that the inhibition of gastric distension caused by AUV is based on the inhibition of vagal-dependent receptive relaxation. It appears that the diminished size of the anterior side caused by AUV makes the ulcer crater small, thereby minimizing the noxious effect of gastric juice or physical irritation by a coarse particle of chow on the ulcerated area. The shrunken mucosa, leading to the small ulcer crater, allows easy coverage of the ulcer surface by the regenerating epithelium. Recently, our group (20) found that contraction of granulation tissue plays an important role in the healing of gastric ulcers. It is possible that granulation tissue contracts easily under the conditions in which gastric relaxation is inhibited. Indeed, the histological observations clearly indicate that the length of the ruptured muscularis mucosa of the anterior side was clearly shorter than that of the posterior side in AUV animals. This observation suggests that tissue contraction is considerably accelerated by AUV in the anterior side. To confirm this hypothesis, the effect of a liquid diet, which prevents relaxation of the stomach or shortens the relaxation time compared with solid food, was determined. As a result, the healing of ulcers on both the AUV and vagally intact sides was found to be enhanced with a liquid diet at nearly the same rate, compared with that in the case of normal chow. The numbers of calories in the liquid diet and chow ingested per day were the same, so this effect is unrelated to a possible increase in nutrients.

We conclude that AUV significantly accelerates the healing of gastric ulcers on the denervated side through inhibited gastric acid secretion and relaxation.

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