Effect of Elcatonin on Experimental Gastric and Duodenal Ulcers

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Abstract—The antiulcer action of elcatonin, an analogue of natural eel calcitonin, was compared with that of cimetidine, secretin and solcoseryl. Elcatonin (3 to 10 u/kg, s.c.) inhibited the development of gastric ulcers induced by pylorus ligation, water-immersion stress, aspirin and reserpine and duodenal ulcers induced by cysteamine in rats. Moreover, once daily injections of elcatonin (1 to 10 u/kg/day, s.c.) promoted the healing of acetic acid-induced chronic gastric ulcers not only in rats but in dogs. The healing effect persisted after the cessation of administrations. Cimetidine (30 to 100 mg/kg, p.o.) inhibited the development of gastric ulcers induced by water-immersion stress, aspirin and reserpine and duodenal ulcers induced by cysteamine in rats. However, once daily administrations of cimetidine (30 to 100 mg/kg/day, p.o.) did not show significant effect on acetic acid-induced chronic gastric ulcers in rats. Secretin (30 to 100 u/kg, s.c.) inhibited the development of gastric ulcers induced by pylorus ligation, water-immersion stress, aspirin and reserpine in rats, but was not effective on cysteamine-induced duodenal ulcers and acetic acid-induced chronic gastric ulcers in rats. Solcoseryl (2 ml/kg, s.c.) inhibited only the development of water-immersion stress-induced gastric ulcers in rats. These results suggest that elcatonin is different from these reference drugs in its properties of action on experimental ulcers. Mechanisms of the antiulcer action of elcatonin which has a superior effect on experimental ulcers are discussed.

Calcitonin is a polypeptide consisting of 32 amino acids which has not only a lowering effect on serum levels of Ca and P, but also has an inhibitory effect on gastric acid secretion (1) and some experimental ulcers (2–6).

Elcatonin, a synthetic analogue of natural eel calcitonin, has been reported to possess hypocalcemic activity comparable to that of natural eel calcitonin and has been reported to be physicochemically more stable than the natural product (7, 8). We have reported that elcatonin markedly inhibits gastric acid secretion (9) and the development of the water-immersion stress-induced ulcers (10) in rats.

In the present study, we investigated the effect of elcatonin on various experimental ulcers in comparison with those of cimetidine, secretin and solcoseryl in order to clarify the characteristics of the antiulcer action of elcatonin.

Materials and Methods
1. Experimental animals
Male Wistar rats (160–190 g body weight) obtained from the Shizuoka Agricultural Cooperative Association and male Beagle dogs (6 months old) obtained from Toyo Experimental Animal Center were used.

2. Experimental materials
Drugs used were: elcatonin (Toyo Jozo, 6000 elcatonin unit (u)/mg), cimetidine (Smith Kline & Fujisawa), secretin (Eisai), solcoseryl (Taiho), aspirin (Iwaki), reserpine (Daiichi), acetic acid (Wako) and cysteamine hydrochloride (Tokyo Kasei).

Elcatonin was dissolved in citrate buffer (0.37 mg citric acid, 4.63 mg sodium citrate and 7.00 mg sodium chloride in 1 ml distilled water, pH 6.0) containing 0.2% gelatine. Secretin was dissolved in the appended
vehicle. Aspirin was suspended in 1% methylcellulose. Acetic acid was diluted with distilled water. Other drugs were dissolved in saline.

Elcatonin, secretin and solcoseryl were injected subcutaneously (0.1 ml/100 g b.w.), and cimetidine was administered orally or intraduodenaly (1.0 ml/100 g b.w.). To the control groups, the corresponding vehicles were injected subcutaneously.

3. Experimental ulcers

1) Shay ulcers: The pylorus ligation was performed following the procedure of Shay et al. (11). Rats fasted for 48 hr were used, and test drugs were administered subcutaneously or intraduodenally immediately after ligation. The rats were sacrificed 48 hr later and the stomach of each rat was removed. The stomach was incised along the greater curvature and examined for gastric ulcers in the forestomach by the ulcer index of Adami (12). Ulcer index: 0, no lesion; 1, hemorrhagic suffusion; 2, 1–5 small ulcers (<3 mm); 3, many small ulcers (more than 5) or 1 ulcer of marked size; 4, many ulcers of marked size; 5, perforated ulcers.

2) Water-immersion stress-induced ulcers: Rats fasted for 24 hr were placed in a stress cage and immersed to the level of the xiphoid process in a water bath (21±1°C) (13). After 5 hr, the stomach of each rat was removed and slightly inflated by injecting 2–3% formalin solution, and then it was immersed in 2–3% formalin solution for several minutes to fix the inner and outer layers of the gastric walls. The stomach was then incised along the greater curvature. The number of the developed erosions in the glandular portion were counted under a stereoscopic microscope and were determined as the ulcer index. Test drugs were administered subcutaneously or orally just before the water-immersion.

3) Aspirin-induced ulcers: Aspirin (200 mg/kg) was given orally to rats fasted for 24 hr (14). The rats were sacrificed 4 hr later, and the stomach of each rat was examined for ulcers by the same procedure as in the experiment on the water-immersion stress ulcers. Test drugs were administered subcutaneously or orally 30 min before aspirin dosing.

4) Reserpine-induced ulcers: Reserpine (5 mg/kg) was injected intraperitoneally to rats fasted for 24 hr (12). The rats were sacrificed 18 hr later and the stomachs were examined for ulcers by the same procedure as in the experiment on the water-immersion stress ulcers. Test drugs were administered subcutaneously or orally just before reperpine dosing.

5) Cysteamine-induced ulcers: Cysteamine (400 mg/kg) was injected subcutaneously to rats fasted for 24 hr (15). The rats were sacrificed 18 hr later, and the stomach and duodenum were dissected out as a single unit, opened along the greater curvature of the stomach and mesenteric attachment of the duodenum, and examined for the ulcers in the duodenal mucosa. The severity of the lesions was classified according to the following ulcer index: 0, no lesion; 1, petechia; 2, marked hemorrhage; 3, shallow ulcer; 4, deep ulcer; 5, perforated ulcer (16).

6) Acetic acid-induced ulcers in rats (17): Laparotomy by a midline, epigastric incision was made in rats under ether anesthesia. After exteriorizing the stomach, 0.05 ml/rat of 20% acetic acid was injected into the subserosal layer of the anterior wall of the glandular stomach. Then, the abdomen was closed and all rats were maintained conventionally. The rats were sacrificed 20 days later and each stomach was removed. The inner and outer layer of the gastric wall was fixed according to the same procedure as in the experiment on the water-immersion stress ulcers. The stomach was opened along the greater curvature and the length and width of the ulcers were measured. The ulcer index was determined using the product of length and width. Test drugs were administered once daily for 19 days from the operative day.

7) Acetic acid-induced ulcers in dogs (18): Beagle dogs fasted for 24 hr were anesthetized with thiopental-Na (25 mg/kg, i.v.) and were fixed on their back. A gastrofiberscope (Olympus, GFB) was inserted into the stomach and 10% acetic acid (1 ml) was injected into the submucosal layer of the anterior portion of the stomach body under direct vision. After confirmation of the gastric ulcer on the 3rd day, the dogs were grouped into 3 so as to show a similar degree of
ulceration, and test drugs were administered subcutaneously once daily (with the exception of Saturday and Sunday) until the ulcer healed. Observation of the gastric ulcer was carried out twice a week using a gastrofiberscope.

4. Statistics

Statistical significance was determined using Student’s t-test (stress-, aspirin-, reserpine- and acetic acid-induced ulcers) or Mann-Whitney’s U-test (Shay and cysteamine-induced ulcers). P values of 0.05 were considered significant.

Results

1. Shay ulcers: The degree of the ulcers in the control group was characterized by an ulcer index of more than 4. Elcatonin significantly inhibited the development of the ulcers at a dose of 10 u/kg or more, the ulcer index being decreased to 0.7±0.9 from 4.6±0.8 at a dose of 30 u/kg (Table 1). Secretin also showed the inhibitory activity at a dose of 100 u/kg. Solcoseryl (1 and 2 ml/kg) and cimetidine (3 to 100 mg/kg) failed to inhibit the development of the ulcers.

2. Water-immersion stress-induced ulcers: Rats in the control group suffered from about 30 erosions in the glandular stomach. Elcatonin markedly inhibited the development of the ulcers at doses of 3, 10 and 30 u/kg (Table 2). The inhibition rates were 52.8, 73.5 and 93.7%, respectively. Solcoseryl (2 ml/kg), secretin (30 and 100 u/kg) and cimetidine (30 and 100 mg/kg) also showed significant inhibitory activity.

3. Aspirin-induced ulcers: Rats in the control group suffered from about 9 erosions in the glandular stomach. Elcatonin significantly decreased the ulcer index by 50.1, 72.7 and 85.5% at doses of 3, 10 and 30 u/kg, respectively (Table 3). Secretin (30 and 100 u/kg) and cimetidine (30 and 100 mg/kg) also showed inhibitory activity; cimetidine was particularly effective at 100 mg/kg, showing an inhibition of 93.9%. Solcoseryl (1 and 2 ml/kg) did not show significant activity.

4. Reserpine-induced ulcers: Effect on reserpine-induced ulcers is shown in Table 4. In the control group, about 15 erosions were observed in the glandular stomach. Elcatonin inhibited the development of the erosions by 46.0 and 87.5% at doses of 10 and 30 u/kg, respectively. Secretin (100 u/kg) and cimetidine (100 mg/kg) significantly in-

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Table 1. Effect of elcatonin, solcoseryl, secretin and cimetidine on Shay’s ulcers in rats

| Drugs          | Dose  | Route | No. of rats | Ulcer index (Mean±S.D.) | Inhibition (%) |
|----------------|-------|-------|-------------|-------------------------|---------------|
| Control (Vehicle) |       | s.c.  | 15          | 4.6±0.8                 |               |
| Elcatonin      | 1 u/kg| s.c.  | 15          | 4.5±0.8                 | 2.2           |
|                | 3 u/kg| s.c.  | 15          | 3.9±1.2                 | 15.2          |
|                | 10 u/kg| s.c. | 15          | 3.5±1.0*                | 23.9          |
|                | 30 u/kg| s.c. | 15          | 0.7±0.9*                | 84.1          |
| Control (Saline) |       | s.c.  | 10          | 4.6±0.5                 |               |
| Solcoseryl     | 1 ml/kg| s.c. | 10          | 4.2±0.9                 | 8.7           |
|                | 2 ml/kg| s.c. | 10          | 4.1±1.0                 | 10.9          |
| Secretin       | 30 u/kg| s.c. | 10          | 4.0±1.1                 | 11.0          |
|                | 100 u/kg| s.c. | 10         | 3.6±1.1*                | 21.7          |
| Control (Saline) |       | i.d.  | 7           | 4.4±0.8                 |               |
| Cimetidine     | 3 mg/kg| i.d. | 7           | 3.9±1.1                 | 12.9          |
|                | 10 mg/kg| i.d. | 7           | 3.7±1.1                 | 16.1          |
|                | 30 mg/kg| i.d. | 7           | 3.3±1.5                 | 25.6          |
|                | 100 mg/kg| i.d. | 7          | 4.0±1.3                 | 9.5           |

Ulcers were produced by pylorus ligation for 18 hr in 48 hr-fasted rats. Each drug was given subcutaneously or intraduodenally immediately after pylorus ligation. * Significant difference from the control (P=0.05, Mann-Whitney’s U-test).
hibited the ulceration by 44.9 and 53.1%, respectively. Solcoseryl (1 and 2 ml/kg) failed to inhibit the ulceration.

5. Cysteamine-induced ulcers: Cysteamine produced an oval ulcer near the pylorus in the duodenum. Elcatonin significantly inhibited the development of the ulcers at a dose of 3 u/kg or more, the ulcer index being decreased to 1.2±1.1 from 2.8±0.7 at a dose of 30 u/kg (Table 5). The inhibition rates calculated from the ulcer index were 17.9, 21.4, 21.4 and 57.1% at doses of 1, 3, 10 and 30 u/kg, respectively. Cimetidine also showed the inhibitory activity at doses of 30 and 100 mg/kg. Solcoseryl (1 and 2 ml/kg) and secretin (30 and 100 u/kg) failed to show any significant effect.

6. Acetic acid-induced ulcers in rats: Rats in the control group had defined ulcers with an area of about 10 mm² (ulcer index: 11.8) on the 20th day after injection of acetic acid. Elcatonin significantly decreased the ulcer index of 8.7±4.9 to 1.6±1.3 (Table 6). Cimetidine also showed the inhibitory activity at doses of 30 and 100 mg/kg. Solcoseryl (1 and 2 ml/kg) and secretin (30 and 100 u/kg) failed to show any significant effect.

### Table 2. Effect of elcatonin, solcoseryl, secretin and cimetidine on stress-induced gastric ulcers in rats

| Drugs     | Dose  | Route | No. of rats | Ulcer index (Mean±S.D.) | Inhibition (%) |
|-----------|-------|-------|-------------|--------------------------|----------------|
| Control (Vehicle) |       | s.c.  | 15          | 29.9±8.8                 |                |
| Elcatonin | 1 u/kg| s.c.  | 23          | 26.1±8.5                 | 12.7           |
|           | 3 u/kg| s.c.  | 14          | 14.1±6.3*                | 52.8           |
|           | 10 u/kg| s.c.  | 15          | 7.9±4.3*                 | 73.6           |
|           | 30 u/kg| s.c.  | 15          | 1.9±1.9*                 | 93.7           |
| Control (Saline) |       | s.c.  | 10          | 32.3±6.5                 |                |
| Solcoseryl | 1 ml/kg| s.c.  | 10          | 29.8±8.1                 | 7.7            |
|           | 2 ml/kg| s.c.  | 10          | 20.9±7.7*                | 35.3           |
| Secretin  | 30 u/kg| s.c.  | 10          | 15.4±4.2*                | 52.3           |
|           | 100 u/kg| s.c. | 10          | 15.8±3.9*                | 51.1           |
| Cimetidine| 30 mg/kg| p.o. | 10          | 6.7±2.3*                 | 79.3           |
|           | 100 mg/kg| p.o. | 10          | 4.5±3.2*                 | 86.1           |

Ulcers were produced by water (21 °C) immersion and restraint stress for 5 hr in 24-hr fasted rats. Each drug was given subcutaneously or orally immediately before stress. * Significant difference from the control (P<0.05, Student's t-test).

### Table 3. Effect of elcatonin, solcoseryl, secretin and cimetidine on aspirin-induced gastric ulcers in rats

| Drugs     | Dose  | Route | No. of rats | Ulcer index (Mean±S.D.) | Inhibition (%) |
|-----------|-------|-------|-------------|--------------------------|----------------|
| Control (Vehicle) |       | s.c.  | 15          | 8.7±4.9                  |                |
| Elcatonin | 1 u/kg| s.c.  | 15          | 7.6±4.4                  | 12.9           |
|           | 3 u/kg| s.c.  | 14          | 4.4±3.3*                 | 50.1           |
|           | 10 u/kg| s.c. | 13          | 2.4±2.0*                 | 72.7           |
|           | 30 u/kg| s.c. | 15          | 1.3±1.9*                 | 85.5           |
| Control (Saline) |       | s.c.  | 10          | 9.9±3.9                  |                |
| Solcoseryl | 1 ml/kg| s.c.  | 10          | 8.7±4.7                  | 21.1           |
|           | 2 ml/kg| s.c.  | 10          | 6.9±4.0                  | 30.3           |
| Secretin  | 30 u/kg| s.c.  | 10          | 5.6±4.3*                 | 43.4           |
|           | 100 u/kg| s.c. | 10          | 5.0±2.6*                 | 50.5           |
| Cimetidine| 30 mg/kg| p.o. | 10          | 1.6±1.3*                 | 83.8           |
|           | 100 mg/kg| p.o. | 10          | 0.9±0.7*                 | 93.9           |

Ulcers were produced by giving 200 mg/kg (orally) of aspirin to 24-hr fasted rats. Animals were sacrificed 4 hr after administration of aspirin. Each drug was given subcutaneously or orally 30 min before aspirin treatment. * Significant difference from the control (P<0.05, Student's t-test).
Table 4. Effect of elcatonin, solcoseryl, secretin and cimetidine on reserpine-induced gastric ulcers in rats

| Drugs          | Dose    | Route | No. of rats | Ulcer index (Mean ± S.D.) | Inhibition (%) |
|----------------|---------|-------|-------------|---------------------------|---------------|
| Control (Vehicle) | s.c.    | 19    | 15.6 ± 7.0  |                           |               |
| Elcatonin      | 1 u/kg  | s.c.  | 19          | 12.3 ± 6.8                | 21.2          |
|                | 3 u/kg  | s.c.  | 19          | 10.8 ± 6.0                | 30.8          |
|                | 10 u/kg | s.c.  | 19          | 8.4 ± 7.5*                | 48.0          |
|                | 30 u/kg | s.c.  | 19          | 2.0 ± 2.5*                | 87.5          |
| Control (Saline) | s.c.    | 10    | 14.7 ± 6.5  |                           |               |
| Solcoseryl     | 1 ml/kg | s.c.  | 10          | 12.5 ± 6.9                | 15.0          |
|                | 2 ml/kg | s.c.  | 10          | 12.4 ± 8.0                | 15.7          |
| Secretin       | 30 u/kg | s.c.  | 10          | 10.5 ± 7.7                | 30.6          |
|                | 100 u/kg| s.c.  | 10          | 8.1 ± 5.7*                | 44.9          |
| Cimetidine     | 30 mg/kg| p.o.  | 10          | 8.3 ± 6.8                 | 43.5          |
|                | 100 mg/kg| p.o.  | 10          | 6.9 ± 5.7*                | 53.1          |

Rats fasted for 24 hr were treated with reserpine (5 mg/kg, intraperitoneally) and sacrificed 18 hr later. Each drug was given subcutaneously or orally immediately before reserpine treatment. * Significant difference from the control (P=0.05, Student's t-test).

Table 5. Effect of elcatonin, solcoseryl, secretin and cimetidine on cysteamine-induced duodenal ulcers in rats

| Drugs       | Dose    | Route | No. of rats | Ulcer index (Mean ± S.D.) | Inhibition (%) |
|-------------|---------|-------|-------------|---------------------------|---------------|
| Control (Vehicle) | s.c.    | 15    | 2.8 ± 1.2   |                           |               |
| Elcatonin   | 1 u/kg  | s.c.  | 15          | 2.3 ± 1.1                 | 17.9          |
|             | 3 u/kg  | s.c.  | 15          | 2.2 ± 0.7*                | 21.4          |
|             | 10 u/kg | s.c.  | 15          | 2.2 ± 1.2*                | 21.4          |
|             | 30 u/kg | s.c.  | 15          | 1.2 ± 1.1*                | 57.1          |
| Control (Saline) | s.c.    | 13    | 2.5 ± 1.2   |                           |               |
| Solcoseryl  | 1 ml/kg | s.c.  | 15          | 2.1 ± 1.1                 | 16.0          |
|             | 2 ml/kg | s.c.  | 12          | 2.0 ± 1.0                 | 20.0          |
| Cimetidine  | 30 mg/kg| p.o.  | 17          | 1.2 ± 0.8*                | 52.0          |
|             | 100 mg/kg| p.o.  | 16          | 1.1 ± 1.0*                | 56.0          |
| Control (Saline) | s.c.    | 10    | 2.8 ± 1.6   |                           |               |
| Secretin    | 30 u/kg | s.c.  | 10          | 3.3 ± 1.1                 | -17.9         |
|             | 100 u/kg| s.c.  | 10          | 3.0 ± 1.7                 | -7.1          |

Rats fasted for 24 hr were treated with cysteamine (400 mg/kg, subcutaneously) and sacrificed 18 hr later. Each drug was given subcutaneously or orally immediately before cysteamine treatment. * Significant difference from the control (P=0.05, Mann-Whitney's U-test).

index by 40.7, 48.3 and 46.6% at doses of 1, 3 and 10 u/kg/day, respectively (Table 6). Moreover, these inhibition rates were kept on the 5th day after cessation of successive administrations (Table 7). Solcoseryl (1 and 2 ml/kg/day), secretin (30 and 100 u/kg/day) and cimetidine (30 and 100 mg/kg/day) did not show the inhibitory activity.

7. Acetic acid-induced ulcers in dogs:
Ulcers in the control group healed on the 37th day after injection of acetic acid (Table 8). Elcatonin (10 u/kg/day) shortened the healing period to 28.9 days. In dogs treated with secretin (10 u/kg/day), the healing period was 34 days, which was not significantly different from that of control dogs.
Elcatonin inhibited the development of acute gastric ulcers induced by pylorus ligation, water-immersion stress, aspirin and reserpine and acute duodenal ulcers induced by cysteamine at subcutaneous doses of 3 to 10 u/kg in rats. Moreover, once daily injections of elcatonin (1 to 10 u/kg/day, s.c.) promoted the healing of acetic acid-induced chronic gastric ulcers not only in rats but in dogs. It has been reported that porcine and salmon calcitonin have antiulcer actions in rats: porcine calcitonin inhibited Shay ulcers by 2 subcutaneous injections of 1 u/body (2) and reserpine-, serotonin- and

### Table 6. Effect of elcatonin, solcoseryl, secretin and cimetidine on healing of acetic acid-induced gastric ulcers in rats

| Drugs      | Dose  | Route | No. of rats | Ulcer index (Mean±S.D.) | Inhibition (%) |
|------------|-------|-------|-------------|-------------------------|----------------|
| Control (Vehicle) | s.c.  | 15    | 11.8±6.4    |                         |                |
|            | 1 u/kg| s.c.  | 15          | 7.0±5.2*                | 40.7           |
|            | 3 u/kg| s.c.  | 15          | 6.1±4.2*                | 48.3           |
|            | 10 u/kg| s.c. | 14          | 6.3±2.4*                | 46.6           |
| Solcoseryl | 1 ml/kg| s.c. | 15          | 9.6±5.8                 | 18.6           |
|            | 2 ml/kg| s.c. | 15          | 8.8±6.4                 | 25.4           |
| Secretin   | 30 u/kg| s.c. | 14          | 8.8±3.8                 | 25.4           |
|            | 100 u/kg| s.c. | 14          | 8.3±4.6                 | 28.7           |
| Cimetidine | 30 mg/kg| p.o. | 15          | 9.8±6.6                 | 16.9           |
|            | 100 mg/kg| p.o. | 15          | 7.8±4.7                 | 33.9           |

Ulcers were produced by injecting 0.05 ml of 20% acetic acid into the subserosal layer of the rat glandular stomach. Animals were sacrificed 20 days after operation. Each drug was administered subcutaneously or orally once a day for 19 days. *Significant difference from the control (P=0.05, Student's t-test).

### Table 7. Change in acetic acid-induced gastric ulcers after cessation of elcatonin injections in rats

| Treatments         | No. of rats | Ulcer index (Mean±S.D.) | Inhibition (%) |
|--------------------|-------------|-------------------------|----------------|
| Day 1              |             |                         |                |
| Control            | 11          | 14.7±8.4                |                |
| Elcatonin 10 u/kg  | 11          | 4.9±2.2*                | 66.7           |
| Day 5              |             |                         |                |
| Control            | 11          | 11.1±8.9                |                |
| Elcatonin 10 u/kg  | 11          | 3.4±2.9*                | 69.4           |

Ulcers were produced by injecting 0.05 ml of 20% acetic acid into the subserosal layer of the rat glandular stomach. Elcatonin was administered subcutaneously once a day for 19 days. Animals were sacrificed 1 or 5 days after last administration. * Significant difference from the control (P=0.05, Student's t-test).

### Table 8. Effect of elcatonin and secretin on healing of acetic acid-induced gastric ulcers in dogs

| Drugs      | Dose  | Route | No. of dogs | Days of healing (Mean±S.D.) |
|------------|-------|-------|-------------|-----------------------------|
| Control    |       |       | 6           | 37.0±3.7                    |
| Elcatonin  | 10 u/kg| s.c.  | 7           | 28.9±4.6*                   |
| Secretin   | 10 u/kg| s.c.  | 6           | 34.0±3.5                    |

Ulcers were produced by injecting 1.0 ml of 10% acetic acid into the submucosal layer of stomach in 24 hr-fasted dogs, and the healing process of the ulcers was observed endoscopically. Test drugs were administered subcutaneously for 5 consecutive days every week. * Significant difference from the control (P=0.05, Student's t-test).

### Discussion

Elcatonin inhibited the development of acute gastric ulcers induced by pylorus ligation, water-immersion stress, aspirin and reserpine and acute duodenal ulcers induced by cysteamine at subcutaneous doses of 3 to 10 u/kg in rats. Moreover, once daily injections of elcatonin (1 to 10 u/kg/day, s.c.) promoted the healing of acetic acid-induced chronic gastric ulcers not only in rats but in dogs. It has been reported that porcine and salmon calcitonin have antiulcer actions in rats: porcine calcitonin inhibited Shay ulcers by 2 subcutaneous injections of 1 u/body (2) and reserpine-, serotonin- and
gastrin-induced ulcers by 2 intramuscular injections of 2 u/body (3), and salmon calcitonin inhibited restraint (4), indomethacin (5) and acetic acid-induced ulcers (6) by a subcutaneous injection of 16, 10 and 1 u/kg, respectively. The inhibitory potency of elcatonin on these experimental ulcers was considered similar to that of porcine and salmon calcitonin.

In this study, we compared the antulcer effect of elcatonin with those of representative antiulcer agents, cimetidine, secretin and solcoseryl. The mode of the antulcer action of cimetidine, a histamine H2-receptor antagonist, is considered attributable to the inhibition of gastric secretion to block H2-receptor at parietal cells (19). However, another mechanism has been indicated because cimetidine shows an inhibitory effect on some experimental gastric ulcers in doses which do not inhibit the gastric secretion (19, 20). Secretin, a gastrointestinal hormone consisting of 27 amino acids, is reported to have an antulcer effect by inhibiting the gastric secretion due to its antigastrin effect (21) and solcoseryl, an extract of calf-blood, is reported to show an antulcer effect by a catalytic action on the tissue respiration (22). In the present studies, cimetidine (30 to 100 mg/kg, p.o.) inhibited the development of water-immersion stress-, aspirin- and reserpine-induced acute gastric ulcers and the development of cysteamine-induced acute duodenal ulcers in rats, but did not show a significant effect on pylorus ligation-induced acute gastric ulcers and acetic acid-induced chronic gastric ulcers in rats. These results almost agreed with those by Okabe et al. (19). Secretin inhibited the development of acute gastric ulcers induced by pylorus ligation, water-immersion stress, aspirin and reserpine in rats, which supported the results by Matsuo et al. (21). However, secretin did not show a significant effect on acetic acid-induced chronic gastric ulcers and cysteamine-induced acute duodenal ulcers. Solcoseryl inhibited only the development of water-immersion stress-induced acute gastric ulcers in rats. In contrast with these drugs, elcatonin showed inhibitory activity on all experimental ulcer models. It has been shown that the ulcer is susceptible to relapse after cimetidine therapy (23). Elcatonin might not produce such a rebound effect after clinical medication, since the healing effect of elcatonin on acetic acid-induced ulcers persisted after the cessation of successive administrations.

The cause of peptic ulcers is considered due to the unbalance between aggressive and defensive factors in the gastric mucosa (24). Aggressive factors include the secretion of acid and pepsin, etc. Defensive factors include the resistance of mucus and mucosa and the gastric mucosal barrier, etc. Elcatonin inhibited gastric secretion (9) and Shay ulcers which are considered to be produced by digestion due to accumulated gastric juice (11). One of the modes of the antulcer action of elcatonin might be related to the inhibitory effect on gastric secretion, namely the inhibition of aggressive factors. On the other hand, elcatonin promoted the healing of acetic acid-induced ulcers which was not affected by antacids and anti-cholinergic agents (18) and showed the inhibitory activity on cysteamine-induced ulcers whose pathogenic mechanism was caused not only by the acceleration of gastric acid secretion but by the decrease of mucus secretion from Brunner's glands (25, 26). Furthermore, elcatonin inhibited reserpine-induced ulcers whose pathogeny was scarcely related with the effect on gastric secretion (27). These results suggest that elcatonin acts by another mechanism besides the inhibition of gastric secretion. Elcatonin inhibited water-immersion stress- and aspirin-induced ulcers at a lower dose than that needed to inhibit Shay ulcers. The pathogeny of water-immersion stress-induced ulcer is thought to involve the increase of gastric motility and the decrease of gastric mucosal blood flow, etc. (28). The pathogeny of aspirin-induced ulcer involves the back diffusion of hydrogen ion to break the gastric mucosal barrier (29). In addition to these reports, elcatonin increased hexosamine and uronic acid content, which were associated with defensive mechanisms in gastric mucosa of both intact and water-immersed rats (H. Ohno, unpublished data). So the antulcer effect of elcatonin might be also associated with the actions on some of the above defensive factors in the stomach.
and duodenum.

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