INFLUENCE OF SURGICAL SYMPATHECTOMY ON GASTRIC SECRETION AND ULCERATION IN RATS

Yutaka KASUYA, Teizo MURATA and Susumu OKABE*
Department of Chemical Pharmacology, Faculty of Pharmaceutical Sciences, University of Tokyo, Bunkyo, Tokyo 113, Japan
*Department of Applied Pharmacology, Kyoto College of Pharmacy, 5 Goryo-Nakauchi, Yamashina, Kyoto 607, Japan
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Abstract—The influences of sympathectomy on gastrointestinal mucosa, gastric secretion, acute or chronic gastric ulcers were studied in rats. Under ether anesthesia, sympathectomy was performed by surgical removal of the celiac ganglion. Surgical sympathectomy per se produced no pathological changes in the gastrointestinal tract as determined by macroscopical observation 3, 10 or 20 days after operation. The volume of gastric juice and pepsin output were not influenced by the sympathectomy but gastric acid output was significantly increased in pylorus-ligated rats. The sympathectomy worsened the stress- and the indomethacin-induced ulcer and delayed the healing of chronic gastric ulcers a little but not significantly, and had no deteriorative influence on the reserpine-induced ulcers. In contrast, Shay ulcers, aspirin- or serotonin-induced ulcers were significantly aggravated by sympathectomy. The loss of H+ ions and gain of Na+ ions in the gastric juice of pylorus-ligated and aspirin-treated rats were not affected by sympathectomy.

Chemical or surgical sympathectomy has been performed by many workers in attempts to clarify the significance of sympathetic nervous system on gastric secretion or ulceration in man and experimental animals, but the data were controversial (1–6). Oberhelman et al. (3) observed the hypersecretion of gastric juice after surgical sympathectomy in dogs and suggested that deprivation of the sympathetic nerve supply to the stomach in ulcer patients worsens the condition. On the other hand, Rivilis (6) has reported that immunosympathectomy failed to increase the acid secretion in pylorus-ligated rats, whereas acute gastric ulcers or hyperemia developed.

Surgical sympathectomy was carried out in the present study to determine whether or not the sympathetic nervous system does have a significant influence on the integrity of gastric mucosa, secretion and the formation of various acute or chronic ulcers in rats.

MATERIALS AND METHODS

Male Donryu and Wistar strain rats were used.

Sympathectomy: Sympathectomy was performed according to the method established by one of the present authors (Y.K.) (7). Briefly, with the rat under ether anesthesia, the abdomen is incised and the celiac ganglion area exposed by dislocating the stomach, spleen and hepatic lobes. After careful elimination of fatty tissues around the ganglion, sympathectomy is performed by removing the ganglion and cutting the postsynaptic nerve trunk
along the celiac arteries. To ensure the denervation, the connective tissue between the stomach and spleen is also carefully resected. The completeness of sympathectomy is then confirmed by the disappearance of catecholamines from the stomach using fluorescence histochemical techniques. No fluorescence was observed 3 days after the operation. As the sham operation, the fatty tissue alone was resected and the celiac ganglion was simply confirmed.

**Examination of pathological changes:** Male Donryu rats, 200-250 g, were used. After sympathectomy or sham operation, the animals were maintained on Oriental rat chow and water *ad libitum*, and sacrificed on the 3rd, 10th or 20th day after the operation. Ten rats were included in each group. Under ether anesthesia the animals were given 0.7 ml of a 5% solution of pontamine sky blue 6 BX dissolved in saline (pH 7.2) in the tail vein 10 min before sacrifice. The stomach and intestine of each rat were excised, inflated by injecting 20 ml of 1% formalin solution, and immersed into 1% formalin solution for 10 min. These organs were incised along the greater curvature and mucosal changes were observed under the dissecting microscope (10×). The stomach, except for Shay ulceration, was treated with 1% formalin solution and examined under the dissecting microscope for the presence of ulceration.

**Gastric secretory studies:** Two days after sympathectomy, male Donryu rats, 180-200 g, were deprived of food for 24 hr and with the animals under ether anesthesia, the pylorus was ligated. Four hr later, the animals were sacrificed under ether anesthesia and the stomach of each was excised. The gastric contents were collected and analyzed for volume and acidity. The acidity was determined by titrating of the gastric juice with 0.1 N NaOH to pH 7.0 using the autoburette (Radiometer); acid output was expressed as µEq/hr. The pepsin activity was determined by Anson's method (8); pepsin output was expressed as mg tyrosine/hr.

**Ulcerogenic procedures:** Three days after sympathectomy or sham operation, the following acute ulcers were produced.

**Stress ulcers:** Male Donryu rats, 220-250 g, were used. Sympathectomized or sham operated rats were placed in individual restraint cages and immersed in a water bath (23°C) up to the xiphoid process for 7 hr (9). At the end of the stress, the animals were sacrificed by a blow on the head. The stomach of each was excised, incised along the greater curvature and examined for ulcers in the glandular portion. The sum of the length (mm) of each ulcer was used as an ulcer index.

**Shay ulcers:** Male Wistar rats, 200-320 g, were used. Sympathectomized or sham operated rats were deprived of food for 48 hr and the pylorus was ligated (10). The animals were sacrificed 12 hr later, the stomach of each was excised and the ulcerated area (mm²) in the forestomach was measured, summed and arbitrarily graded into 5 degrees as an ulcer index as follows.

| Ulcerated area (mm²) | 1-12 | 13-25 | 26-37 | 38-50 | >51 or perforation |
|----------------------|------|-------|-------|-------|-------------------|
| Ulcer index          | 1    | 2     | 3     | 4     | 5                 |

**Aspirin-induced ulcers:** Male Donryu rats, 180-200 g, were used. Sympathectomized
or sham operated rats were deprived of food for 24 hr, after which the pylorus was ligated. Aspirin (Sanko) suspended in 1% carboxymethylcellulose (CMC) solution was given orally at the dose of 100 mg/kg to the rats 15 min after pylorus ligation (11). The animals were sacrificed 7 hr later by an overdose of ether and the stomach was excised. The gastric contents were collected through the esophagus and analyzed for volume, acidity, Na\(^+\) and K\(^+\) ion concentrations and pepsin activity. The concentration of Na\(^+\) and K\(^+\) ions was measured by a flame photometer. The stomach of each rat was examined for ulcers in the glandular portion and the sum of the length of each ulcer (mm) was used as an ulcer index.

**Indomethacin-, reserpine- or serotonin-induced ulcers:** Male Donryu rats, 180–200 g, were used. Sympathectomized or sham operated rats were deprived of food 24 hr and then given either indomethacin (Merck) at the dose of 20 mg/kg s.c., reserpine (Daiichi) at the dose of 7.5 mg/kg i.p. or serotonin creatinin sulfate (Wako) at the dose of 20 mg/kg s.c.. These animals given indomethacin were sacrificed 7 hr later and those given reserpine or serotonin were sacrificed 18 hr later and ulcers in the glandular stomach were observed. The sum of the length (mm) of each indomethacin- or reserpine-induced ulcer or area (mm\(^2\)) of each serotonin-induced ulcer was used as an ulcer index.

**Acetic acid-induced ulcer:** Male Donryu rats, 200–230 g, were used. After sympathectomy or sham operation, 20% acetic acid solution (0.015 ml) was injected into the anterior gastric wall at the junction of the body of the glandular stomach and the antrum (12). After closure of the incised abdomen, the animals were maintained on Oriental rat chow and water ad libitum and were sacrificed by a blow on the head 14 days after the operation. The ulcerated area (mm\(^2\)) was measured as an ulcer index. Healing index is expressed as follows,

\[
\text{Healing index (\%)} = \frac{\text{ulcer index in sham operated rats} - \text{ulcer index in sympathectomized rats}}{\text{ulcer index in sham operated rats}} \times 100
\]

The person observing or measuring the gastrointestinal mucosa or ulcers was not aware of which animals had been treated. Student’s t-test was employed to determine the statistical significance of the data obtained in this study.

**RESULTS**

**Pathological changes in the stomach and intestine**

There were no appreciable mucosal changes in the stomach and intestine both in sympathectomized and sham operated rats on the 3rd, 10th or 20th day after the operation.

**Gastric secretion**

As can be seen in Table 1, the acid output in sympathectomized rats was significantly increased as compared to the sham operated animals, while gastric volume and pepsin output were not influenced by sympathectomy.

**Influences on acute ulcers**

As shown in Table 2, sympathectomy worsened the stress ulcers and the indomethacin-induced gastric ulcers but such was not significant. No deteriorative influence on the
reserpine-induced ulcers was noted. In contrast, Shay ulcers, aspirin- or serotonin-induced ulcers were significantly aggravated by sympathectomy. As to the Shay ulcers, 10 of 12 sympathectomized rats (83%) succumbed to free perforation of the ulcer in the forestomach, whereas only 3 of the 12 sham operated rats died from perforation. Changes in gastric contents of aspirin-treated rats are shown in Table 3. Aspirin significantly reduced to the same extent the acid output in sham operated and sympathectomized rats. In addition, aspirin induced a significant increase in Na+ output in both groups. Gastric Volume, K+ output and pepsin output were not influenced by aspirin administration in each group. In serotonin treated sympathectomized rats, a wide area of hyperemia was observed in the mucosa of glandular stomach. Such changes were never observed in sham operated rats.

**Influence on chronic ulcers**

As shown in Table 4, the ulcer index determined 14 days after the operation was slightly higher in the sympathectomized rats than sham operated rats, thus indicating the slightly delayed healing in the sympathectomized rats; the difference, however, was not statistically significant.
| Rats               | Treatment | No. of rats | Volume (ml) | Acid output (μEq/hr) | Na⁺ output (μEq/hr) | K⁺ output (μEq/hr) | Pepsin output (mg/hr) |
|-------------------|-----------|-------------|-------------|----------------------|--------------------|--------------------|------------------------|
| Sham operated     | Control   | 10          | 11.5±0.4    | 165.8±9.5            | 82.4±8.9           | 13.0±1.2           | 29.9±1.2               |
|                   | Aspirin   | 10          | 10.9±0.4    | 108.8±7.1**          | 110.7±8.9*         | 11.7±0.8           | 30.0±1.6               |
|                   |           |             |             | -5.2                 | -34.4              | +34.3              | -10.0                  | +0.4                   |
|                   | % change from control | | | | | | | |
| Sympathectomized  | Control   | 10          | 11.2±0.7    | 186.8±16.3           | 77.3±5.0           | 11.4±1.3           | 31.9±2.4               |
|                   | Aspirin   | 10          | 12.4±0.6    | 131.8±9.6**          | 126.9±13.8**       | 10.3±1.0           | 36.0±1.8               |
|                   |           |             |             | +10.7                | -29.4              | +64.2              | -9.6                   | +12.9                  |

All values represent mean ± s.e. Three days after sympathectomy aspirin at the dose of 100 mg/kg was given orally immediately after pylorus ligation. The animals were sacrificed 7 hr after aspirin dosing. Significantly different from control values: *P<0.05, **P<0.01. No significant difference was observed between sham operated control and sympathectomized control.
TABLE 4. Influence of surgical sympathectomy on healing of acetic acid gastric ulcer in rats

| Rats                | No. of rats | Ulcer index (mm²) mean±s.e. | Healing index (%) | P value |
|---------------------|-------------|-----------------------------|-------------------|---------|
| Sham operated       | 17          | 12.2±2.0                    |                   |         |
| Sympathectomized    | 14          | 15.9±2.0                    | -30.3             | N.S.    |

Gastric ulcers were formed immediately after sympathectomy and the animals were sacrificed 14 days after operation. N.S.: P > 0.05

DISCUSSION

These studies indicate that surgical sympathectomy per se has no influence on the gastric and intestinal mucosa, under the normal conditions, and as determined by macroscopical observations. However, sympathectomy significantly increased the gastric acid output in pylorus-ligated rats in the 4 hr experiment (Table 1) but not significantly in the 7 hr experiments. (Table 3; control). In this respect, it might be said that, in the 7 hr experiment, because of the accumulation of acid in the gastric lumen, acid secretory rate is inhibited and acid output approaches the plateau level. Therefore, a clear-cut difference cannot be observed in 7 hr experiments between sympathectomized and sham operated groups. This result is inconsistent with the finding of Rivilis (6) who reported no change in gastric secretion after sympathectomy. This difference may be due to the difference in methods of sympathectomy and the period of experiment; Rivilis used an immunological technique and ligated the pylorus only for 2 hr. Whether or not this increase in acid output is due to removal of the inhibitory influence of sympathetic nerves on the vagal nerves is not known at present.

It was of interest that sympathectomy did exert an aggravating influence on certain types of experimental ulcers; i.e., Shay ulcers, aspirin- or serotonin-induced gastric ulcers. It is well known that gastric acid is a necessary factor for the development of Shay or aspirin-induced ulcers (10, 13). Therefore, aggravation of these ulcers with surgical sympathectomy may be the result of increased acid output at the early stage of the ulcerogenic treatment. Aspirin-induced ulcers are considered to be causally related to the increased acid back diffusion through the broken barrier (14). Thus there is the possibility that sympathectomy may have enhanced the back diffusion of acid at the time of aspirin administration, hence the aggravated formation of aspirin-induced ulcers. However, the degree of acid back diffusion caused by aspirin in sympathectomized rats was found to be the same as that in sham operated animals. The pathogenesis of serotonin-induced ulcers has been reported (15, 16), but such remains to be fully elucidated. Aures and Thompson (17) observed that serotonin contents were decreased in the stomach of immunosympathectomized rats. Therefore, sympathetic nerves are probably involved in the protective mechanism in gastric mucosa.

Sympathectomy exerted a slight but not statistically significant deteriorative influence on stress ulcers and indomethacin-induced ulcers, while no appreciable influence was seen on the reserpine-induced ulcers. Concerning stress ulcers, our finding was consistent with
the data reported by Djahanguiri et al. (18) who observed that chemical sympathectomy with 6-hydroxydopamine failed to prevent the stress ulceration in rats. Gupta et al. (19) reported that reserpine-induced ulcers in rats were prevented by chemical sympathectomy with 6-hydroxydopamine. Our present findings do not contradict the results obtained by Gupta et al., in the sense that no aggravation in reserpine-induced ulcers occurred with sympathectomy. Djahanguiri et al. (20) emphasized the role of the sympathetic nervous system on the etiology of indomethacin-induced ulcers in rats. However, our present results suggest that sympathetic nerves do not play any appreciable role on the gastric ulceration induced by indomethacin.

Takagi et al. (12) observed a delayed healing of acetic acid-induced ulcers in rats undergoing a surgical bilateral vagotomy and suggested the importance of vagal innervation on the stomach for healing of chronic ulcers. As seen in the present study, sympathectomy also delayed healing of acetic acid-induced ulcers as compared to sham operation, but the change was slight and statistically insignificant. Surgical vagotomy strongly inhibits gastric secretion, stress ulcers, Shay ulcers and several drug-induced ulcers, i.e., aspirin, indomethacin, reserpine in rats (21-26). In addition, Ellis and Pryse-Davies (27) reported that vagotomy in rats induced gastric dilatation and ulceration 10–12 weeks later. Therefore, it can be tentatively concluded that while sympathetic nerves function in such a way that certain types of acute ulcers are prevented, these nerves do not appear to play so crucial a role as vagus nerves in gastric function.

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