

# Effects of Vagotomy on Histamine Content and Responses to Tetragastrin in the Rat Stomach

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**Summary.** Vagotomy in the rat initially caused a significant reduction in acid secretion of the stomach after operation, with complete recovery noted 4 weeks later. Histamine content in the gastric wall also revealed a similar reduction and recovery after vagotomy. The increase in acid secretion responding to tetragastrin was observed as well to diminish markedly and then recover, over a similar course of time. Although tetragastrin caused a marked reduction of histamine content in the unoperated rat stomach, it caused no significant reduction of histamine content in the vagotomized stomach even in later periods after operation. The recovered gastric acid secretion in the vagotomized stomach might thus not be mediated by histamine. It is therefore suggested that the histamine release by tetragastrin needs the vagal nerve, and a receptor other than  $H_2$ -receptor may mediate the action of tetragastrin in the vagotomized stomach.

## INTRODUCTION

Histamine is a strong secretagogue of gastric acid secretion, and many studies on the physiologic role of gastric mucosal histamine have been performed.<sup>1)</sup> However, the precise role of histamine in acid secretion has not been settled. In the last decade,  $H_2$ -receptor antagonists have been used for treatment of the peptic ulcer patient, while experimental studies on gastric histamine using  $H_2$ -receptor antagonists have been documented. Surgical vagotomy has also been performed for peptic ulcer patients, but the interaction between histamine and the vagal nerve has been generally ignored.

The present study reports the alteration of histamine content, as well as acid output, in the vagotomized rat stomach. The effects of tetragastrin on histamine content in vagotomized stomach are also reported.

## MATERIALS AND METHODS

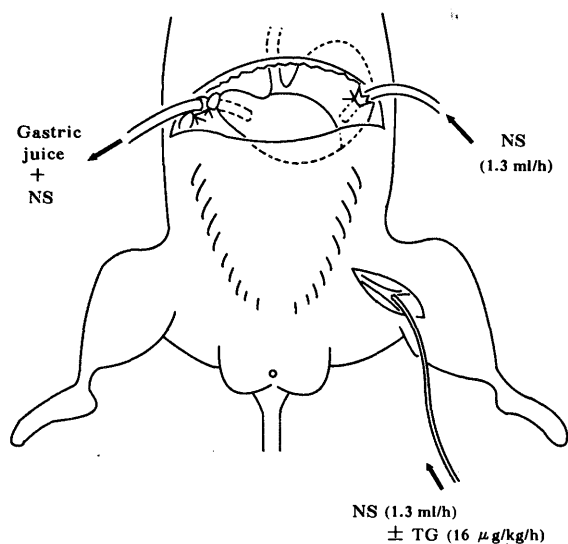
Experiments were performed on male Wistar rats (body weight: 200-250 g). Truncal vagotomy was performed by the procedure shown below, and the gastric acid output and histamine content in gastric wall were measured at 1, 2, 3, 4 and 8 weeks after operation. As the control group, unoperated rats were used. Each group consisted of 9-13 rats.

### Procedure of vagotomy

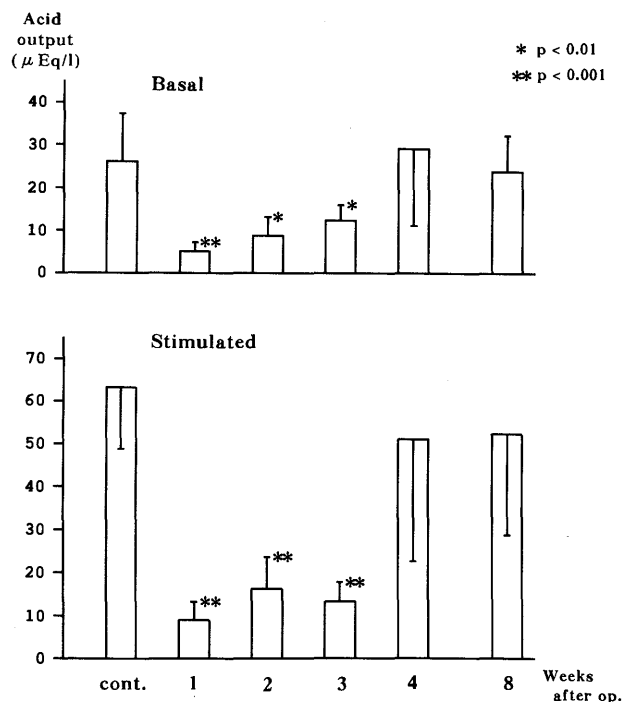
Rats were subjected to laparotomy under pentobarbital anesthesia by an intraperitoneal injection (20 mg/kg). The anterior and posterior trunks of the vagal nerve were cut around the abdominal esophagus. Pyloroplasty was not performed except for one group of rats, in which the gastric histamine content was measured only at 3 days and 1 week after the operation.

### Measurement of acid output

In pentobarbital-anesthetized rats having undergone 24 h fasting, the stomach was perfused continuously with normal saline (1.3 ml/h) through a cannula placed in the forestomach and the gastric juice was collected through another cannula in the antrum inserted from the duodenopylorus. Normal saline (1.3 ml/h) with or without tetragastrin (16  $\mu$ g/kg/h) was administered intravenously from a cannula placed in the femoral vein (Fig. 1). Gastric juice was collected at intervals of 1 h and the acidity was determined by an autotitrator (COMTITE-7<sup>®</sup>; Hiranuma Sangyo Co. Ltd., Tokyo). After 2 h of administration of normal saline, tetragastrin was given for 3 h. The mean values of acid output of two collections in the first 2



**Fig. 1.** Procedures for the collection of gastric juice. NS: normal saline. TG: tetragastrin.



**Fig. 2.** Alterations in acid output after vagotomy. "Basal": the acid output under the continuous administration of normal saline (1.3 ml/h). "Stimulated": the acid output under the continuous administration of tetragastrin (16 µg/kg/h).

h and in the last 2 h were recorded as the basal and the stimulated acid output, respectively.

### Measurement of histamine content

The stomach was taken from pentobarbital-anesthetized rats after 24 h fasting. The whole wall of the gastric corpus and antrum were prepared for histamine measurement with *o*-phthalaldehyde (OPT). Each tissue was homogenized with 0.4 N perchloric acid and extracted by butanol. Extracted histamine was treated with 0.1 N HCl and n-heptane, and then measured by a fluorescence spectrophotometer (Type 650-10; Hitachi Co. Ltd., Tokyo) according to Shore et al.<sup>2)</sup>

In the unoperated rats, the gastric wall was taken at 1, 2 and 3 h after continuous administration of tetragastrin (16 µg/kg/h), and its histamine content was measured.

In the vagotomized rats, the gastric histamine content was measured after 24 h fasting, and after 3 h of continuous administration of tetragastrin (16 µg/kg/h).

### RESULTS

The vagotomized stomach without pyloroplasty was considerably dilated at 1 week after operation, and then improved gradually. Pyloroplasty showed a slight improvement in the gastric dilatation. Neither ulcers nor erosion was observed in the stomach of any group.

#### Alterations in acid output after vagotomy

In unoperated rats, the basal acid output was  $29.9 \pm 14.5$  µEq/h and the stimulated acid output amounted to about twice the basal one:  $60.5 \pm 20.3$  µEq/h. The acid output was reduced especially at 1 week after vagotomy and the stimulatory effect of tetragastrin was insignificant:  $5.3 \pm 1.75$  µEq/h as the basal,  $9.0 \pm 3.74$  µEq/h as the stimulated. At 2 weeks after vagotomy, acid output still showed low values, though a slight recovery was observed:  $9.1 \pm 3.86$  µEq/h as the basal,  $18.8 \pm 8.95$  µEq/h as the stimulated. At 4 weeks and 8 weeks after vagotomy, the acid output revealed high values as in the control group:  $28.8 \pm 19.18$  µEq/h as the basal,  $51.9 \pm 28.33$  µEq/h as the stimulated (4 weeks); and  $24.1 \pm 8.33$  µEq/h as the basal,  $52.3 \pm 13.84$  µEq/h as the stimulated (8 weeks) (Fig. 2).

### Alterations in histamine content after vagotomy

The gastric corpus contained high concentrations of histamine:  $54.6 \pm 11.34 \mu\text{g/g}$ ; the antrum contained considerably lower amounts:  $5.0 \pm 1.24 \mu\text{g/g}$ .

Continuous administration of tetragastrin ( $16 \mu\text{g/kg/h}$ , 3 h) caused a marked reduction in gastric histamine contents:  $15.3 \pm 5.19 \mu\text{g/g}$  in the corpus,  $1.6 \pm 0.38 \mu\text{g/g}$  in the antrum (Fig. 3).

One week after vagotomy, the gastric corpus revealed a significant reduction in histamine contents:  $23.8 \pm 7.37 \mu\text{g/g}$  in the corpus,  $3.4 \pm 1.82 \mu\text{g/g}$  in the antrum (Fig. 4). Furthermore, the continuous administration of tetragastrin caused no significant reduction in histamine in the vagotomized stomach:  $19.9 \pm 7.53 \mu\text{g/g}$  in the corpus,  $2.1 \pm 0.92 \mu\text{g/g}$  in the antrum (Fig. 6).

The vagotomized stomach with pyloroplasty revealed not such low histamine contents in the corpus at 3 days after operation:  $44.5 \pm 10.28 \mu\text{g/g}$  in the corpus,  $2.5 \pm 1.08 \mu\text{g/g}$  in the antrum. However, at 1 week after operation, the gastric corpus contained concentrations of histamine as low as the vagotomized stomach without pyloroplasty:  $32.7 \pm 6.44 \mu\text{g/g}$  in the corpus,  $2.7 \pm 1.34 \mu\text{g/g}$  in the antrum (Fig. 5).

The histamine contents in vagotomized stomach recovered with time, attaining high values comparable to those in the controls in the corpus ( $63.4 \pm 14.62 \mu\text{g/g}$ ) as well as the antrum ( $5.0 \pm 1.50 \mu\text{g/g}$ ) at 4 weeks after operation (Fig. 4). Tetragastrin administration, however, caused no significant reduction in histamine contents in the vagotomized stomach during either period after operation (Fig. 6).

### DISCUSSION

Since Abel and Kubota<sup>3)</sup> reported that histamine was present in the gastric mucosa in relatively high concentrations, many studies have investigated their possible functions. MacIntosh<sup>4)</sup> proposed that histamine in the gastric mucosa might mediate the effect of the vagus upon the secretory action of the parietal cells. Code<sup>5)</sup> suggested its acting as the final common mediator in acid secretion, and Black et al.<sup>6)</sup> supported this view using  $\text{H}_2$ -receptor antagonists. However, Johnson and Aures<sup>7)</sup> reported that secretin, while completely blocking acid secretion, could not block histamine release caused by pentagastrin injection. They proposed that secretin halted gastrin's direct action upon parietal cells, and that therefore histamine was not the final common mediator. Grossman and Konturek<sup>8)</sup> then suggested that parietal cells

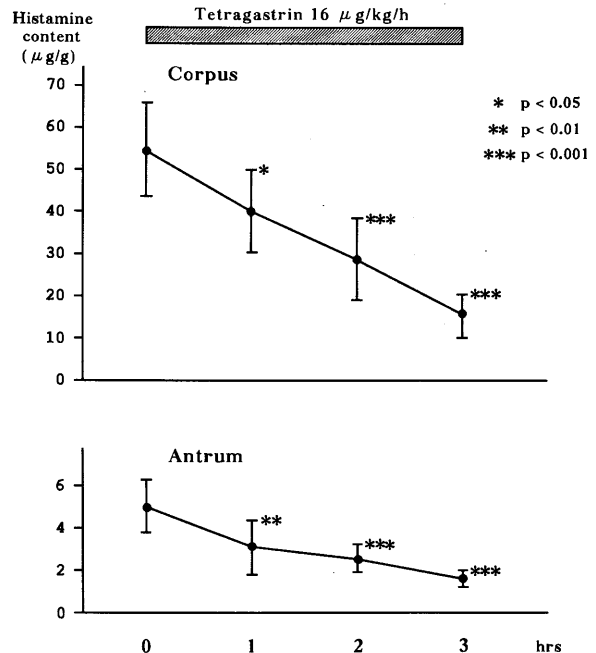


Fig. 3. Changes in the gastric histamine contents during the continuous administration of tetragastrin ( $16 \mu\text{g/kg/h}$ ) intravenously.

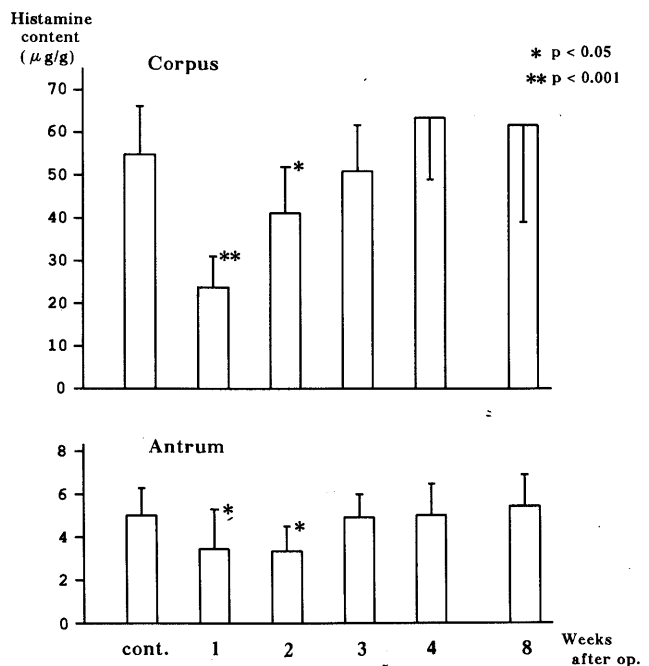


Fig. 4. Alterations in gastric histamine contents after vagotomy without pyloroplasty.

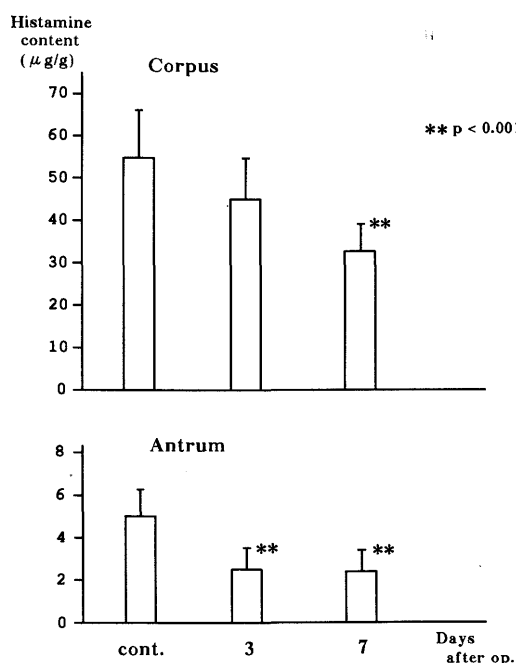


Fig. 5. Alterations in gastric histamine contents in the early period after vagotomy with pyloroplasty.

might possess multiple receptors to gastrin and muscarine beside histamine.

On the other hand, vagotomy has been performed universally as the surgical treatment for peptic ulcer, and it is well known that the vagotomized stomach reveals a marked reduction in acid secretion. However, few studies are available concerning the dynamics of histamine in the vagotomized stomach.

#### Histamine contents after vagotomy

Håkanson and Liedberg<sup>9)</sup> reported an activation of a histamine synthetic enzyme, histidine decarboxylase, in rat oxyntic mucosa after vagotomy. Lundell et al.<sup>10)</sup> reported that gastric histamine increased remarkably in the rat stomach treated with truncal vagotomy with or without pyloroplasty. Kim<sup>11)</sup> also reported similar results and suggested the proliferation of histamine-containing cells using fluorescence histochemistry. These authors supposed that histamine contents might increase as a result of the enhanced gastrin release caused by reduced acid secretion. Troidl et al.<sup>12)</sup> reported that biopsy materials of human gastric mucosa from selectively-vagotomized patients at 6-11 months after operation revealed higher concentrations of histamine than those from

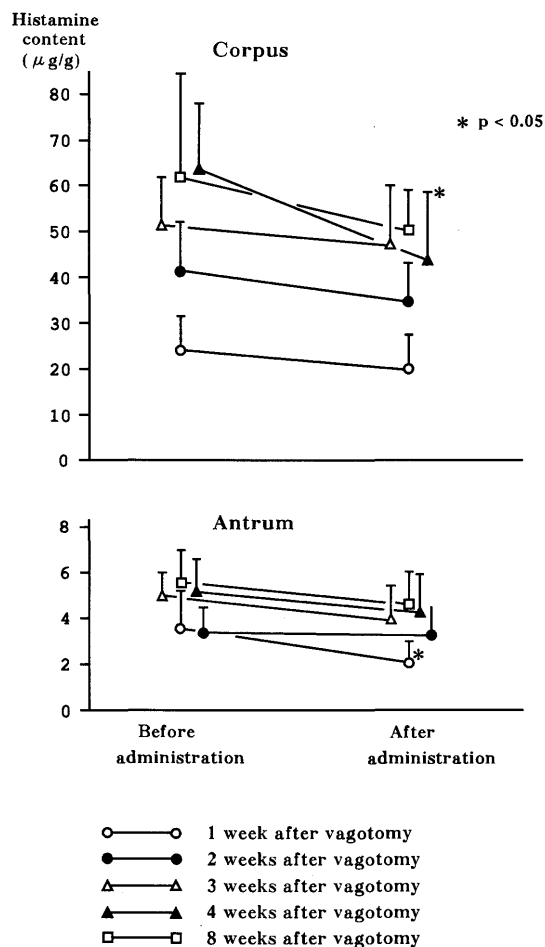


Fig. 6. Effects of tetragastrin on the gastric histamine contents after vagotomy. The gastric histamine contents were measured after 24 h fasting ("Before administration"), and after continuous administration of tetragastrin (16 μg/kg/h for 3 h ("After administration") in each group of periods after vagotomy.

preoperative subjects. They proposed that the increase in gastric histamine was caused mainly by the diminished release of histamine.

On the other hand, Hutson et al.<sup>13)</sup> and Reichle et al.<sup>14)</sup> reported that the histamine of the rat gastric mucosa was not influenced by truncal vagotomy. Recently, Håkanson et al.<sup>15)</sup> observed that vagal denervation reduced the cell density of histamine-containing enterochromaffin-like (ECL) cells, though they did not measure gastric histamine contents. Those studies indicating no increase in histamine content were carried out during a relatively early period after vagotomy (2-3 weeks), though the others indicating an increase in histamine were performed 2-7 weeks after vagotomy. The present study showed

a marked decrease in histamine content in the gastric mucosa within 1-2 weeks after vagotomy. Following this, histamine contents recovered in 1 month after the operation, though not to exceed preoperative values. Therefore, the discrepancies among the above results might be explained by the difference in the times elapsed after the operation when the experiments were made. Acid secretion revealed a similar change as histamine contents after vagotomy in this study. The changes in acid secretion might have considerable effects on the histamine release. Regrettably, however, no measurement of acid output was documented in the above studies, and the interaction between the alterations of histamine and acid secretion has remained unexplained.

The reason for the decrease in histamine content demonstrated in this study was uncertain. The mechanical factors of gastric dilatation might have influenced the histamine metabolism, but these are supposed insignificant, because the present study showed only a slight difference in the histamine content of the stomach between the simply vagotomized group and the vagotomized and pyloroplasticated group. It seems likely that the increase in basal histamine release caused by the insensibility of parietal cells might be correlated to the decrease in histamine content.

#### Responses of histamine to tetragastrin after vagotomy

It is well known that gastrin causes histamine release in many animals.<sup>16-20)</sup> The present study revealed a marked reduction in histamine contents in the gastric antrum as well as gastric corpus after continuous administration of tetragastrin. Lönroth et al.<sup>21)</sup> reported that pentagastrin stimulation caused a reduction of histamine contents in human oxyntic mucosa, but no such change in pyloric mucosa. They proposed that mast cells, which represented the majority of histamine-containing cells in the pyloric mucosa,<sup>22)</sup> were not sensitive to gastrin. However, the reduction of antral histamine by tetragastrin infusion observed in this study suggested that mast cells were also sensitive to gastrin, at least in the rat stomach.

After vagotomy, on the other hand, tetragastrin caused little or no reduction of histamine contents in gastric corpus and antrum. This suggests that vagal innervation is essential for the action of gastrin on histamine release. Lönroth et al.<sup>23)</sup> observed the slight reduction of gastric histamine contents and slight increase in histidine decarboxylase activity by pentagastrin administration in human vagotomized

stomach, whereas the marked reduction of histamine contents and marked increase in the enzyme activity were observed preoperatively. However, they reported previously that, after vagotomy, pentagastrin infusion caused a more significant change in histamine contents in rats,<sup>10)</sup> conversely. The reason for the discrepancy between the results of these authors and ours is obscure.

The recovery of parietal cell sensitivity in the vagotomized stomach seems of importance. Some vagotomized patients have revealed a recovery in acid output within a few years after operation, with some even suffering from recurrent peptic ulceration. Experimental studies using animals have documented that acid secretion after vagotomy recovers earlier than in human cases.<sup>24)</sup> In the present study, the gastric acid output was recovered in 1 month after vagotomy. An increase in acid output by tetragastrin was also observed, though no reduction in histamine contents was noticed. It is thus concluded that after vagotomy, gastrin's action is not mediated by histamine and a receptor or receptors other than H<sub>2</sub>-receptor may be mainly involved in acid secretion.

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