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Vagal Influence on Gastrointestinal Histamine in the Rat

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Introduction

Gastrointestional functions such as secretion and motility under the vagal influence are regulated also by active amines such as serotonin, histamine, etc. and polypeptides such as gastrin, secretin, etc. in connection with the vagus nerve.

Since histamine injected in dog was shown to provoke strong secretion of gastric juice (POPIELSKI 1920)[33], not a few reports have been made of its physiological actions especially in terms of the role of histamine in the gastrointestinal physiology. Nevertheless, in its relation to gastrin it remains whether histamine is the final stimulating factor of gastric secretion in parietal cells[13,21,22,27], there is also much controversy concerning the course followed by histamine liberated from the digestive tract tissues, though histamine in the tract has been examined for alteration under various conditions in connection with the vagus nerve[25,28,27]. As for its cellular localization, it has proved to be mostly distributed in the mucosa of the gastrointestinal tract by the established fluorescence histochemical method with orthophthalaldehyde (OPT)[6]. But the producing cells of histamine still remain partly unexplained. With so many reports of histamine made since comparatively long ago, we are not still uncertain on many points, such as its localization in the gastrointestinal tract, the relationship of its mechanism of liberation to the vagus nerve, and its role of mediator in gastric secretion.

Clinically, minute examination of the relationships of histamine in the digestive tract and the vagus nerve may lead to an elucidation of the pathophysiology of gastro-duodenal ulcers the physiological effect of vagotomy as one course of surgical treatment. Then, for the purpose of making clearer the relationship of histamine in the digestive tract with the vagus nerve, the author carried out an animal experiment, which is reported as follows.

Material and methods

1. Material

Male Wister rats weighing 200–300 g were fasted for 24 hours, but allowed water ad libitum

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prior to each experiment. They were anesthetized with Nembutal (30 mg/kg, i.p.)

2. Methods

1) Electrical vagal stimulation

The abdominal cavity was opened and the abdominal vagus nerves were dissected free and cut just below the diaphragm. The distal cut ends were placed on a bipolar platinum electrode connected to an electrical stimulator delivering monophasic square wave stimuli with a duration of 5 msec and an intensity of 4 volts. The impulse frequency was 10 cycles/sec and continued for 15 minutes. Liquid paraffin was placed over the nerves to prevent drying during the experiment. After stimulation, the various portions of the stomach and duodenum were removed separately and excised and homogenized in acid solution. Blood samples were taken from the portal and femoral veins. Histamine concentration in the tissues and blood samples was determined fluorometrically after appropriate extracts according to the method of SHORE et al[36]. Histochemical demonstration of histamine in the stomach and duodenum was done according to the orthophthalaldehyde technique by HÅKANSON et al[6,10].

2) Gastric secretion

The abdomen was opened and a polyethylene cannula was inserted through the pylorus and then the pylorus was ligated. Electrical vagal stimulation was then done by the method described above. The gastric secretion was collected every 15 minutes, the volume was measured and the total acid was determined by titration against 0.01 N NaOH using pH meter, and the histamine content was determined.

3) Vagotomy

The three experimental groups were divided. Truncal vagotomy alone and truncal vagotomy with pyloroplasty were the operations which were performed in addition to the sham operation (simple laparotomy). Three weeks following the operations, the rats were killed and the various portions of the stomach and duodenum were excised and homogenized in acid solution. Blood samples from the portal and femoral veins were taken for determination of histamine level. Histamine concentrations in the tissues and blood samples were determined fluorometrically by the method of SHORE et al[36].

4) Determination of histamine content (Fig. 1)

Tissues were homogenized in 0.4 N perchloric acid. The homogenate was then centrifuged. A aliquot of the supernatant was added to a glass stoppered shaking tube containing 0.5 ml of 5 N NaOH, 1.5 g of solid NaCl and 10 ml of n-butanol. The tube was shaken for 10 minutes and after centrifugation, the organic phase was added to 5 ml of salt saturated to 0.1 N NaOH and was then shaken for 5 minutes. The tube was then centrifuged and an 8 ml aliquot of the butanol was transferred to a glass stoppered shaking tube containing 4.5 ml of 0.1 N NCl and 15 ml of heptane. After shaking for 5 minutes, the tube was centrifuged. Extracted histamine was measured fluorometrically as described in detail elsewhere by SHORE et al[36].

5) Histochemical demonstration of histamine (Fig. 2)

The tissue pieces were dissected and rapidly frozen at the temperature of liquid nitrogen in an iso-pentane mixture followed by freeze-drying for 5–7 days at −35°C (thermoelectric dryer).

1. Freeze and thaw samples.
2. Samples → 4 ml 0.4 N $HClO_4$.
3. Add to 1st tube containing.
   - 0.5 ml 5 N NaOH
   - 1.5 g NaCl
   - 10 ml Butanol (washed)

   Shake 10 min. Spine 5 min.
4. Transfer 9 ml top phase to tube containing.
   5 ml NaCl saturated 0.1 N NaOH
   Shake 5 min. Spine 3 min.
5. Transfer 8 ml top phase to tube containing.
   - 15 ml Heptane (washed)
   - 4.5 ml 0.1 N HCl

   Shake 5 min. Spine 3 min.
6. Aspirate Heptane
   Transfer 2 ml HCl phase to tube containing.
   0.02 ml 10^{-2} M EDTA
7. Add to these samples.
   - 0.2 ml 2 N NaOH
   - 0.1 ml 1% OPT in methanol

   Stand 4 min.
   0.2 ml 2.5 M H_3PO_4
8. Read on Aminco 360 mμ/450 mμ.

Fig. 1. Histamine assay.

After freeze-drying, the specimen was embedded in paraffin in vacuo (2 hours at 60°C), and then microtome sections were made at 4–7 microns. After cooling, the sections were deparaffinized with a few drops of xylene. A closed glass jar (approximately 500 ml) containing a few mg of o-phthal aldehyde was pre-heated in an oven at 100°C for 10 minutes. The slides with the sections were placed in the jar for 20 seconds. They were taken out and placed in a moisture chamber for 2 minutes and then placed in an oven at 80°C for 5 minutes for drying and stabilization of the fluorophores. The sections were mounted in tetrahydrofurfrylalcohol and analyzed under a fluorescence microscope (light source: Osram HBO 200 high pressure mercury lamp, primary filter: Schott BG 12, secondary filter: Zeiss 50).

The fluorophores were activated under these conditions and emitted blue or yellow light of high intensity.

1. Frozen in isopentane cooled by liquid nitrogen.
2. Freeze-dried in vacum at −35°C. for 5 to 7 days.
3. Infiltrated in vacum with paraffin at 60°C. for 2 hours.
4. Embedded in parraffin.
5. Sectioned at 4 to 7 μ thickness and deparaffinized.
6. Exposed to OPT gas at 100°C. for 20 seconds and then to steam for 2 minutes.
7. Mounted in tetrahydrofurfuryl alcohol.
8. Examined using fluorescence microscope.

Fig. 2. Histamine Fluorescence Histochemistry.

Results

1. Effect of electrical vagal stimulation on histamine concentration in the blood (Fig. 3, Table 1)

1) Histamine concentration in the portal vein blood

The mean value of histamine concentration from the control portal vein blood (non-stimulation group) was 0.087 ± 0.008 μg/ml, while the value obtained just after vagal stimulation was 0.081 ± 0.011 μg/ml. The values obtained 30 and 60 minutes after stimulation were 0.093 ± 0.018 μg/ml and 0.076 ± 0.009 μg/ml respectively, but there was no detectable change in the portal vein histamine concentration before and after vagal stimulation.

2) Histamine concentration in the femoral vein blood

Histamine concentration in femoral vein blood was 0.077 ± 0.009 μg/ml on the average in the control group (non-stimulation group) and 0.059 ± 0.010 μg/ml in the group just after vagal stimulation. It was 0.084 ± 0.007 μg/ml and 0.101 ± 0.024 μg/ml in the 30 and 60 minutes after stimulation groups respectively, and as was the case with the portal vein, no significant difference was observed among the groups.

2. Effect of electrical vagal stimulation on histamine concentration in tissues (Fig. 4, Table 2)

Histamine concentration in tissues was 10.03 ± 1.20 μg/g, 32.72 ± 2.91 μg/g, 10.76 ± 1.92 μg/g

Table 1.

Time after Stimulation	Histamine concentration (μg/ml)	
	Portal vein	Femoral vein
Control (No stimulation)	0.087±0.008	0.077±0.009
0	0.081±0.011	0.059±0.010
30 min.	0.093±0.018	0.084±0.007
60 min.	0.076±0.009	0.101±0.024

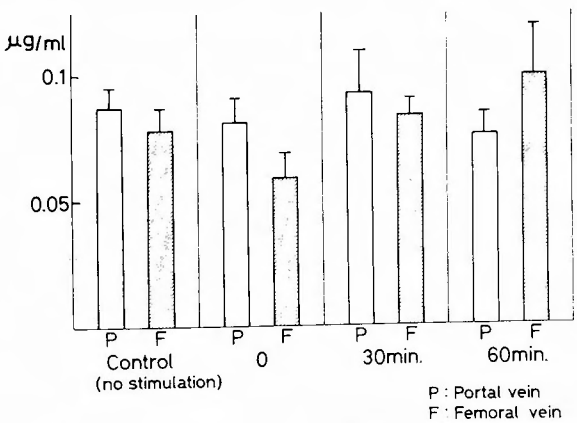


Fig. 3. Changes in the histamine concentration of the blood after electrical vagal stimulation.

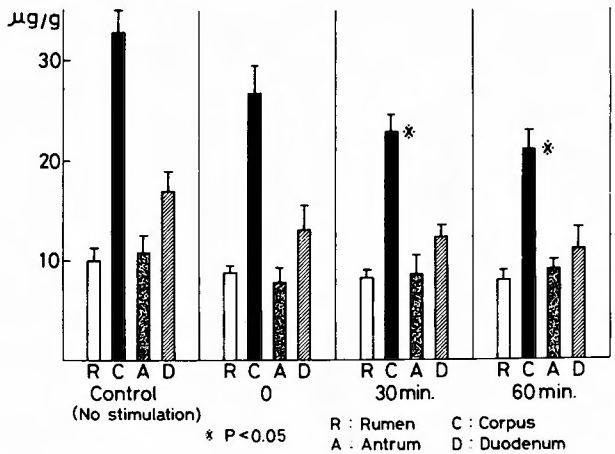


Fig. 4. Changes in the histamine concentration of tissues after electrical vagal stimulation.

and 17.07±2.00μg/g in the rumen, body, antrum and duodenum respectively in the control group, being highest in the body. Starting just after stimulation, histamine concentration in each tissue showed a tendency to decrease, becoming more remarkable with time, being significant especially in the body (22.79±1.83 μg/g and 20.12±2.08 μg/g, 30 and 60 minutes after stimulation respectively). A similar decreasing tendency was observed in the rumen and duodenum, but to a less degree. In the antrum, histamine concentration was lowest just after stimulation and tended to increase slightly 30 to 60 minutes afterwards.

3. Effect of electrical vagal stimulation on histamine content in gastric juice (Fig. 5, Fig. 6)

In the control group (non-stimulation group), histamine output in gastric juice decreased gradually with dissection of the vagus nerves and was lowest 30 minutes after, reaching a plateau thereafter. In the electrical stimulation group, it decreased with the dissection of the vagus nerves but increased significantly with electrical stimulation and thereafter decreased abruptly, reaching near the control value 30 minutes later. A similar tendency was observed in gastric secretion. Namely in the control group, gastric secretion showed a decrease, which became greater with dissection of the vagus nerves, but increased remarkably with electrical stimulation and thereafter decreased abruptly. However, no particular correlation was observed for hista-

Table 2.

Time after Stimulation	Histamine concentration (μg/g)			
	Rumen	Corpus	Antrum	Duodenum
Control (No stimulation)	10.03±1.20	32.72±2.91	10.76±1.92	17.07±2.00
0	8.82±0.68	26.87±2.55	7.53±1.70	13.13±2.37
30 min.	8.12±0.70	22.79±1.83*	8.60±2.06	12.25±1.30
60 min.	8.04±1.01	20.12±2.08*	8.91±0.94	11.10±2.22

* $P<0.05$

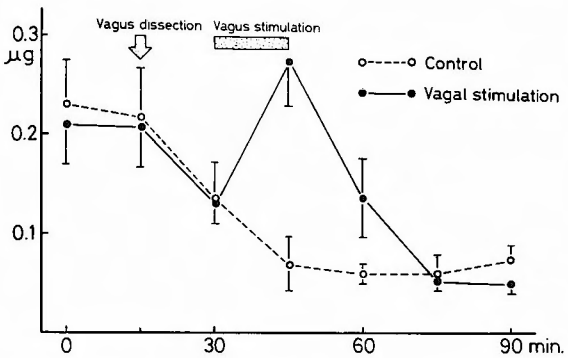


Fig. 5. Effect of electrical vagal stimulation on histamine content in the gastric juice.

mine concentration.

4. Observation of histamine by fluorescence histochemical method (electrical vagal stimulation)

In control rats, a large number of yellow-blue fluorescent cells were observed in the epithelium of the body. The fluorescence was abundant in the basal layer of the mucous membrane (these cells were identified as enterochromaffin-like cells), and similar but lesser fluorescences were present in the antrum mucosal layer. A considerable number of strong yellow fluorescent cells were present both near the mucosal surface and in the submucosa of the whole stomach and duodenum (Fig. 7, Fig. 8(a)). After electrical vagal stimulation, the number of yellow-blue histamine fluorescences in the mucosal layer of the body clearly decreased, while in the mucosal surface layer and submucosal layer strong yellow histamine fluorescences suffered no remarkable alteration (Fig. 8(b)).

5. Effect of vagotomy on histamine concentration in the blood (Fig. 9, Table 3)

1) Histamine concentration of the portal vein blood

Histamine concentration in portal vein blood was $0.074 \pm 0.002\ \mu g/ml$ on the average in the control group (sham operation), being $0.069 \pm 0.004\ \mu g/ml$ and $0.070 \pm 0.002\ \mu g/ml$ in the vagotomy and vagotomy+pyloroplasty groups respectively. However, no significant difference

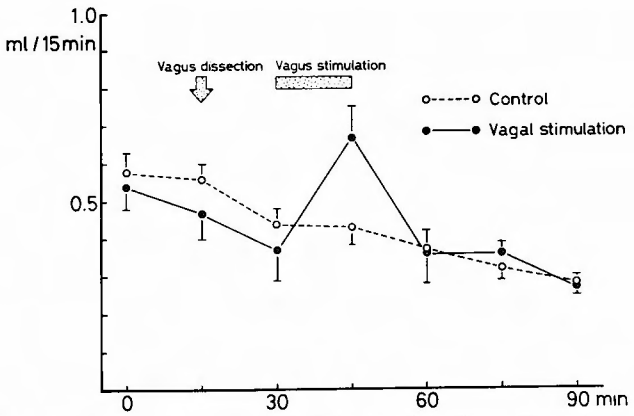


Fig. 6. Effect of electrical vagal stimulation on the volume of gastric secretion.

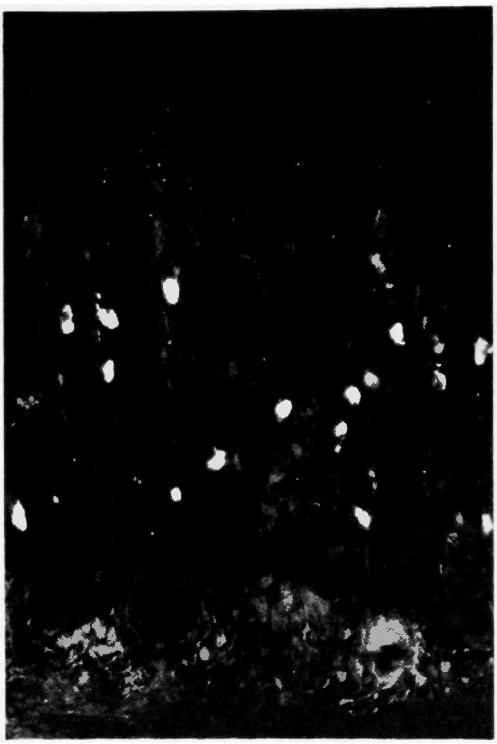


Fig. 7. Fluorescence histochemical demonstration of histamine.
Antrum of normal rat.
The yellow-blue fluorescent cells are observed in the mucosa.

was observed among any of the groups.

2) Histamine concentration in the femoral vein blood

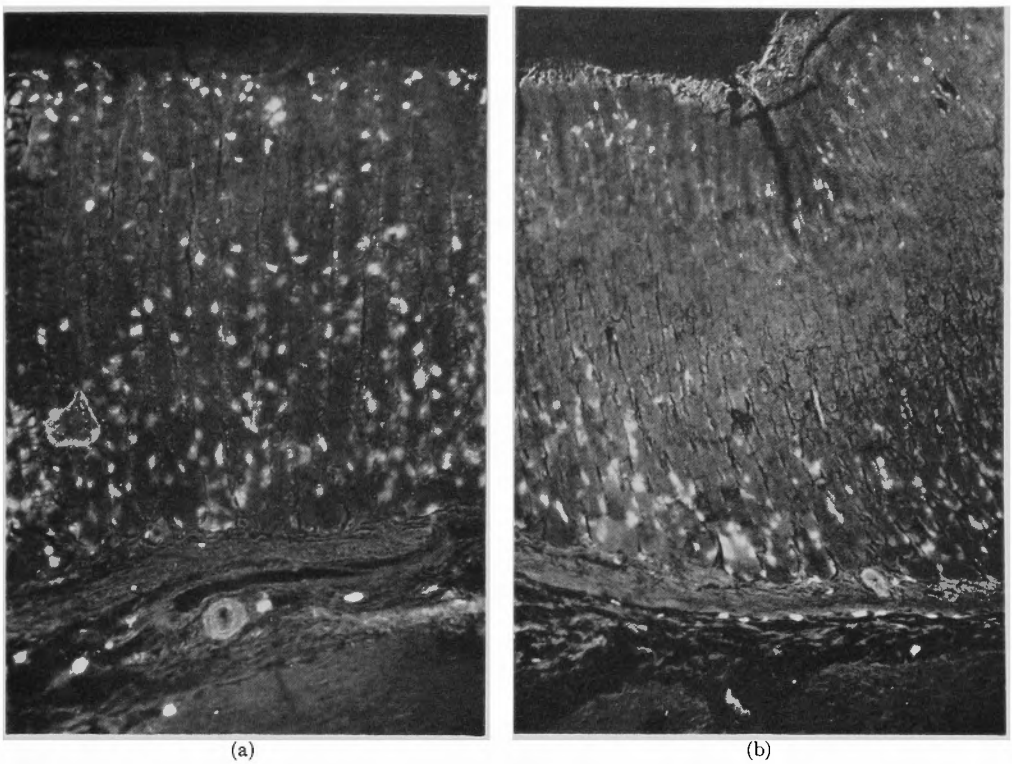
Histamine concentration in femoral vein blood was $0.071\pm0.02\,\mu g/ml$ on the average in the control group (sham operation), being $0.065\pm0.003\,\mu g/ml$ and $0.076\pm0.008\,\mu g/ml$ in the vagotomy and vagotomy+pyloroplasty groups respectively. However, as was the case with the portal venous blood, no significant difference was observed among any groups.

6. Effect of vagotomy on histamine concentration in tissues (Fig. 10, Table 4)

Histamine concentration in tissues three weeks after the operation was $8.29\pm0.84\,\mu g/g$ (control group), $6.95\pm0.82\,\mu g/g$ (vagotomy group) and $5.23\pm0.63\,\mu g/g$ (vagotomy+pyloroplasty

Table 3.

Operation	Histamine concentration ($\mu g/ml$)	
	Portal vein	Femoral vein
Sham operation	0.074±0.002	0.071±0.002
Truncal vagotomy	0.069±0.004	0.065±0.003
Truncal vagotomy +pyloroplasty	0.070±0.002	0.076±0.008



(a) (b)

Fig. 8. Fluorescence histochemical demonstration of histamine.
(a) Gastric body of normal rat.
The yellow-blue fluorescent cells are located mainly basally in the mucosa and the strong yellow fluorescent cells are seen near the mucosal surface and in the submucosa.
(b) Gastric body of rat after electrical vagal stimulation.
The fluorescent cells located mainly basally in the mucosa are apparently decreased, whereas the fluorescent cells near the mucosal surface and in the submucosa are not remarkably changed.

group) in the rumen, and tended to decrease in the vagotomy and vagotomy+pyloroplasty groups to a little greater extent than in the control group, but with no significant difference. In the body, $28.10 \pm 3.10\ \mu g/g$ (control group), $38.46 \pm 3.39\ \mu g/g$ (vagotimy group) and $33.46 \pm 0.93\ \mu g/g$

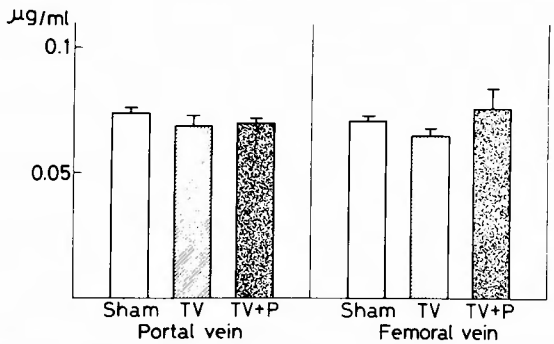


Fig. 9. Changes in the histamine concentration of the blood after vagotomy.

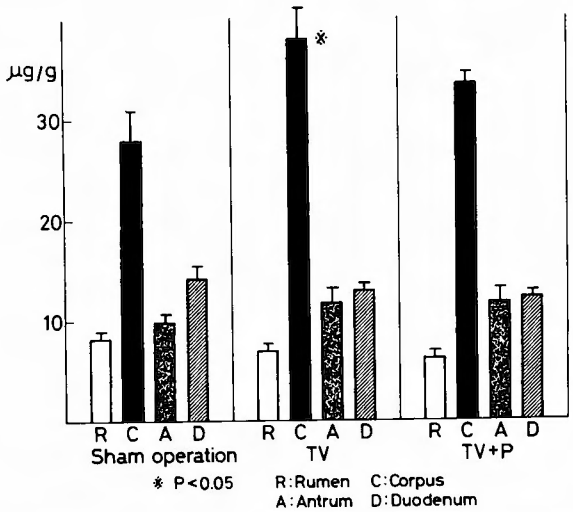


Fig. 10. Changes of the histamine concentration in tissues after vagotomy.

(vagotomy+pyloroplasty group), and especially in the vagotomy group a significant difference was observed. In the antrum, it was 9.92±0.80 μg/g (control group), 11.76±1.57 μg/g (vagotomy group) and 11.79±1.61 μg/g (vagotomy+pyloroplasty group), and also in vagotomy and vagotomy+pyloroplasty groups a slightly increasing tendency was observed, but not any significant difference. In the duodenum, it was 14.25±1.34 μg/g (control group), 13.07±0.74 μg/g (vagotomy group) and 12.33±0.66 μg/g (vagotomy+pyloroplasty group), and tended to decrease in the vagotomy+pyloroplasty group to a little greater extent than in the control group, but no significant difference was observed.

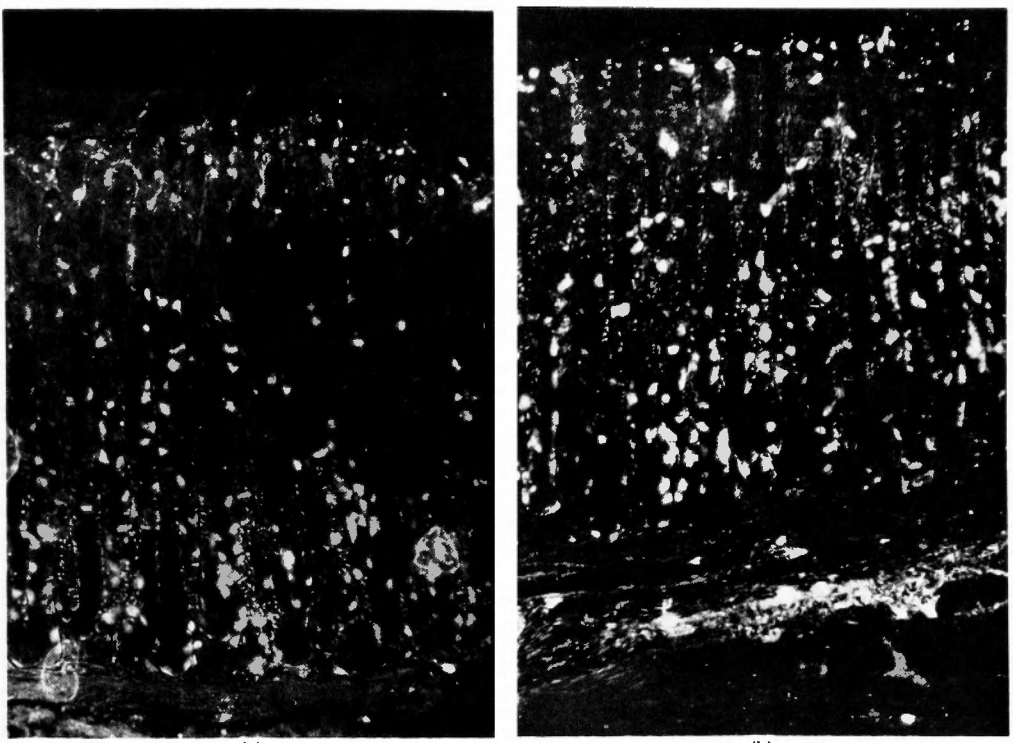
7. Observation of histamine by fluorescence histochemical method (vagotomy)

Following operations (vagotomy and vagotomy+pyloroplasty groups), the number of histamine fluorescences in the mucosal layer of the body considerably increased (Fig. 11 (b)) as compared with the sham operation group (Fig. 11 (a)), but between vagotomy and vagotomy+pyloroplasty groups, no remarkable change was observed. Strong yellow histamine fluorescences in the submucosal layer and surface of mucosal layer was not altered detectably in any operation group.

Table 4.

Operation	Histamine concentration (μg/g)			
	Rumen	Corpus	Antrum	Duodenum
Sham operation	8.29±0.84	28.10±3.10	9.92±0.80	14.25±1.34
Truncal vagotomy	6.95±0.82	38.04±3.39*	11.76±1.57	13.07±0.74
Truncal vagotomy +pyloroplasty	6.23±0.63	33.46±0.93	11.79±1.61	12.33±0.66

* $P<0.05$



(a) (b)

Fig. 11. Fluorescence histochemical demonstration of histamine.
(a) Gastric body of control rat (after sham operation).
As in Fig. 8(a), the yellow-blue fluorescent cells located mainly basally in the mucosa and the strong yellow fluorescent cells near the mucosal surface and in the submucosa are seen.
(b) Gastric body of rat after truncal vagotomy.
The fluorescent cells located basally in the mucosa are considerably increased.

Discussion

1. Cellular localization of gastrointestinal histamine

The significance of histamine in the gastrointestinal tract and of histamine containing cells can vary largely with the animal species[8,40] and the knowledge of this cellular localization of histamine is necessary for understanding of its role in the physiology of gastric secretion. Indeed, the fluorescence-perceiving method using the condensation reaction of histamine with OPT as published by SHORE et al[36], in fact enabled JUHLIN et al[23] to observe the localization of histamine under fluorescence microscope, but this method was methodologically unstable and difficult to reproduce. EHINGER et al[5,16] established a more stable fluorescence histochemical method for histamine with OPT. HÅKANSON et al[10] using this method, examined systematically the cellular localization of histamine in various kinds of animal species. According to these authors, in the rat and mouse gastric histamine is mainly localized in the enterochromoffin-like (ECL) cells of mucosa in accordance with the distribution of histidine decarboxylase (HDC). There-

fore, in these species histamine is reportedly formed and stored in the ECL cells. On the contrary, in other animals, histamine fluorescence is not observed in the ECL cells but only in the mast cells of submucosa and surface of mucosa and no histidine decarboxylase is found in the gastric mucosa. In man, HÅKANSON et al[11] and MOHRI et al [32]reported that the gastrointestinal tract histamine was localized only in the mast cells while TOBE and TANAKA[41] reported histamine localization in the parietal cells themselves.

In rats, the author observed in the same manner as HÅKANSON et al yellow-blue fluorescence cells mainly in the mucosa of the gastric body and strong yellowish fluorescence cells in the gastro-duodenal surface and submucosal layer. The former can be considered histamine fluorescence of the ECL cells and the latter that of the mast cells as defined by HÅKANSON[10].

2. Effect of electrical vagal stimulation on histamine in the gastrointestinal tract

There is not yet an established opinion on the effect of direct stimulation of the vagus nerve itself on the gastrointestinal tract histamine, but it is a well-known fact that the histamine content of gastric mucosa depends on the balance of its rate of formation and its rate of liberation and that the histamine in tissues can vary with various conditions. For example, feeding in rats can cause a remarkable decrease in the gastric histamine[24], but dogs[18], cats[19] etc. cannot be so influence. Insulin[26,28] or gastrin[16,17,34,38,39] stimulation in rats also brings about a decrease.

The course followed by histamine as liberated from tissues remains unexplained in part, the possible courses include 1) its destruction, 2) its binding or rebinding and 3) its loss via the blood stream or gastric juice[14]. A special study should be made of histamine in blood and gastric juice closely related with gastric secretion.

There are not so many reports on the study of blood histamine while stimulating gastric secretion, and most of them gave negative results. IRVINE et al[20] reported that no alteration in the blood histamine was observed while stimulating the gastric secretion with alcohol or insulin and BORN[11] obtained similar results in cats. CARDIS[12], on the other hand, reported increased blood histamine with pentagastrin administered in man. Naturally, tissue histamine liberation is possible even if no alteration is found in the blood histamine. In his own experiment, the author observed some alteration of the tissue histamine with electrical vagal stimulation without alteration in the portal and femoral venous histamine.

The presence of a small quantity of histamine in gastric juice has already been reported by MACINTOSH[31] and CODE[3] in dogs and by EMMELIN and KAHLSON[7] in cats and dogs, respectively. These authors concluded that the gastric histamine decreased gradually with various vagal stimulations (central or peripheral). However, it did not come to take part in the secretory process in view of very few discharges of histamine from tissues into the gastric juice thanks to the gastric mucosal barrier.

The author's results of electrical vagal stimulation showed that the tissue histamine obviously decreased (the rate of decrease was especially remarkable in the gastric body) and histochemically this was observed in terms of the decrease in histamine fluorescence in mucosal ECL cells of the body with little change in that for mast cells. No alteration was observed in the blood histamine determined simultaneously. But under the same conditions, gastric histamine increased remarka-

bly under vagal stimulation and at the same time gastric secretion increased correlatively.

In other words, histamine liberated from the gastric tissues under vagal stimulation is not discharged into the blood, but directly into the gastric juice in close relation with the gastric secretion. However, it remains unexplained by what mechanism histamine is so discharged or whether or not all of the discharges of histamine is due to the stimulation of parietal cells. This requires further examination.

3. Effect of vagotomy on histamine in the gastrointestinal tract

There are a few reports in which the influence of vagotomy on the digestive tract histamine was studied. HUTSON et al[19] and HÅKANSON et al[12] described that in rats the digestive tract histamine was not influenced at all by truncal vagotomy and REICHLE et al[35] published similar results. The latter suggested that in case of combination with a drainage procedure (pyloroplasty or gastrectomy), the decrease in the doudenal and jejunal histamine level without any alteration in gastric histamine is closely related to the alteration of gastrointestinal motility due to vagal denervation and loss of the pyloric sphincter mechanism. As already described, it can be imagined that the cellular localization of gastric histamine varies and differs in significance according to locations, so that study should also be made of the alteration pattern in each location.

The author's results showed that after vagotomy the histamine level showed little change in the non-glandular gastric region and antral portion. The largest change was found in the gastric body and histochemically this was observed in terms of an increase in the histamine fluorescence of gastric body mucosal ECL cells with no remarkable change in that of the mast cells. The difference between this group and the combined pyloroplasty group was not remarkable and the drainge procedure did not have as great an influence as reported by REICHLE[35]. LUNDELL[30] reported that gastric histamine increased remarkably with truncal vagotomy+ pyloplasty, a finding which is almost in coincidence with the author's results. LUNDELL[29,30] ascribed this augmentation to the increased HDC activity[14] due to the disappearance of the inhibiting factor and an increase in liberation of the stimulating factor (perhaps gastrin)[15].

TROIDEL et al[42] demonstrated that gastric histamine obviously increased one year after complete selective vagotomy. This is the first report that human gastric mucosal histamine was altered due to vagotomy.

In other words, it can be imagined that gastric mucosal histamine is less liberated by vagotomy, tending to be retained in the tissues and that a close relationship is found between the decrease in gastric secretion after vagotomy and alteration of the tissue histamine.

Summary

The effects of electrical vagal stimulation and vagotomy on gastrointestinal histamine content were evaluated in rats.

The histamine content in the gastrointestinal tract especially in the body of the stomach, as determined fluorimetrically after appropriate extraction, was found to significantly decrease in rats following direct electrical stimulation of the vagus. Whereas there was no detectable change

in the histamine concentration in either portal or femoral vein blood before and after vagal stimulation, the histamine content in the gastric juice secreted during vagal stimulation was significantly increased.

Histochemically, in rats in which the vagus was stimulated electrically, there was a marked decrease of fluorescent mucosal cells (enterochromaffin-like cells), while no change was seen in the fluorescent cells of the submucosa and surface of the mucosa (mast cells).

These findings suggest that histamine released from the mucosa of the stomach in response to electrical vagal stimulation does not pass into the blood but directly into the gastric juice.

Following vagotomy, the histamine content increased remarkably in the gastric body, but between truncal vagotomy alone and truncal vagotomy with pyloroplasty, there was not any significant difference.

Histochemically, in vagotomized rats, there was found to be an increase of fluorescent cells in the gastric body compared to that in sham operated rats, but no significant change in the fluorescent cells of the submucosa and surface of the mucosa.

From the above mentioned findings, it can be suggested that histamine in the gastrointestinal tract is closely related under a strong vagal influence with gastric secretion.

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和文抄録

迷走神経の胃腸管ヒスタミンに及ぼす影響

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胃腸管の分泌，運動等の機能は，迷走神経の影響下に行なわれているが，この迷走神経による調節以外にもセロトニン，ヒスタミン等の活性アミンや，ガストリン，セクレチンをはじめとするポリペプタイドが，迷走神経と関連しつつ胃腸管の機能を調節している．特にヒスタミンに関しては，強力な胃液分泌作用が古くから注目され，その生理作用について多くの報告があるにもかかわらず，局在，遊離機構等については，不明な点が多くある．又，胃腸管ヒスタミンと迷走神経の関連性の究明は，臨床面においては，胃十二指腸潰瘍の病態生理あるいは，その外科的治療法の1つである迷走神経切離術の生理作用の解明にも参考となり得る．

そこで著者は，胃腸管ヒスタミンと迷走神経との関連性をより明らかにすべく，ラットを用いて実験を行なった．ラットの迷走神経電気刺激により，組織中ヒスタミンは減少傾向を示し，特に胃体部では，有意の減少を示した．一方，血中ヒスタミン濃度には，特に変化を認めなかった．胃液中ヒスタミン量は，電気刺激直後に著明に増加した．螢光組織化学的には，胃体部粘膜のヒスタミン螢光細胞（ＥＣＬ細胞）は明らかに減少した．迷走神経切離後では，胃体部ヒスタミンは増加傾向を示したが，血中ヒスタミン濃度には変化は認められなかった．螢光組織化学的にも，胃体部粘膜のヒスタミン螢光細胞は増加した．

以上の結果により，胃腸管ヒスタミンは，迷走神経の強い影響下にあって，胃液分泌に密接に関係していることが示唆された．