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EXPERIMENTAL STUDIES ON DEVELOPMENTAL MECHANISM OF ACUTE HEMORRHAGIC GASTRIC ULCERS WITH EMPHASIS ON THE EFFECTS OF HISTAMINE*)

By

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ABSTRACT

Studies to elucidate the mechanism responsible for histamine effects on the development of acute hemorrhagic ulcers were undertaken using laboratory animals, i. e. a control group consisting of rats with chronic gastric fistula, V. B_6 deficient diet group, cimetidine administered group and vagotomized group. The respective groups were subjected to cold restraint and the degree of hemorrhage, erosion, gastric acid secretion, gastric mucosal histamine content and state of microvasculature of gastric mucosa were observed over time, and the following results were obtained.

1. There was a decrease in the degree of hemorrhage and erosion in the V. B_6 deficient diet and cimetidine administered groups and the vagotomized group.
2. Gastric acid secretion was significantly decreased in all groups subjected to cold restraint for up to 60 minutes.
3. The gastric mucosal histamine content was significantly decreased in the control and cimetidine administered groups after cold restraint for 30 minutes. In the V. B_6 deficient diet group, the content decreased to about 1/3, but failed to demonstrate a significant difference. The vagotomized group showed a two-fold increase, which after cold restraint for 120 minutes decreased significantly.
4. The microvasculature of the gastric mucosa in the control group was poorly visualized by FITC-dextran method and presented a static appearance. In the other three groups, the capillaries of the gastric mucosa were well visualized and no static pattern was observed.

The above findings suggest that histamine in the gastric mucosa is released by cold restraint and acts upon microcirculation within the gastric mucosa rather than upon gastric acid secretion, causing stasis and mucosal devitalization, and thus assumes a role in the development of ulcer.

INTRODUCTION

Since the use of histamine in the induction of ulcers in laboratory animals by Hay et al.[1] in 1942, it has been used widely in efforts to elucidate the developmental mechanism of ulcer. On the other hand, Thunberg[2] and Håkanson et al.[3] have reported that histamine is widely

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distributed within the mucosa of the digestive tract, especially in the area where parietal cells are present. Thus, attention has been focussed on its relationship with gastric acid secretion.

Ritchie et al.[4] have reported that inhibition of histamine synthesis has prevented the development of stress ulcer, and it is claimed that the histamine H_2 receptor antagonist developed by Black et al.[5] has anti-ulcer and ulcer therapeutic effects. Thus, attention is being focussed on the involvement of endogenous histamine in the development of stress ulcer.

There is, at present, no consensus on the role of histamine in the induction of stress ulcer between the gastric acid secretion theory and vascular theory.

The authors, using cold restraint rats, reviewed the state of gastric acid secretion, histamine volume in the gastric mucosa and the microvasculature of the gastric mucosa in an effort to elucidate the mechanism of histamine effects upon the development of stress ulcer, and also studied the ulcer preventing effects of histamine H_2 receptor antagonist and vagotomy.

MATERIALS AND METHOD

Material: Male Wistor rats about two months after gastrostomy (chronic gastric fistula) by Borella's Method[6] and weighing appoximately 250 g were classified into 4 groups.

a) Control group: Those subjected to gastrostomy only.

b) V. B_6 deficient diet group: Those fed a V. B_6 free diet (Oriental Kobokogyo Co.) prepared according to the method of Kahlson et al.[7] for 3 weeks after which subcutaneous injections of semicarbazide (Nakarai Kagaku Yakuhin Co.) were administered in doses of 50 mg/kg × 2/day for 3 days prior to the experiment.

c) Histamine H_2 receptor antagonist (cimetidine) administered group: Those administered a single injection of cimetidine (Tagamet®) 48 mg/kg in the tail veine 30 minutes prior to the experiment.

d) Vagotomized group: Those subjected to bilateral truncal vagotomy and pyloroplasty at time of gastrostomy.

Method: All groups with the exception of the V. B_6 deficient diet group were fed a standard pellet diet. After a 24 hour fasting, the rats were put into restraint cages and placed in a cold room maintained at 4°C for 30 to 120 minutes after which observation of the following points was carried out at prescribed time.

(Ⅰ) Hemorrhage and erosion

Macroscopic observation was made of the state of hemorrhage and erosion of the gastric mucosa after being subjected to cold restraint for periods of 30, 60 and 120 minutes.

(Ⅱ) Gastric acid secretion

The stomach was thoroughly washed with physiolosical saline to eliminate food residue in the stomach prior to commencing fasting. Upon completion of cold restraint, the stomach was immediately washed again with 10 ml of diluted NaOH solution with pH 8.5. A 2 ml aliquot of gastric fluid was collected and with an autoburette titrated down to pH 7.0 using 0.005N NaOH solution after which the total acid was determined.

(Ⅲ) Histamine content in gastric mucosa

Upon completion of cold restraint test, the stomach was excised and the gastric mucosa of the parietal cell containing region was removed by scraping. From this histamine was extracted using Amberlite CG 50 resin according to the method of Wada et al.[8] After OPT treatment the intensity of fluorescense was measured by a spectrofluorophotometer (Shimadzu RF 501).

(Ⅳ) Microvasculature and red blood cell distribution in gastric mucosa

Upon completion of cold restraint, a single dose of 1 ml of FITC-dextran 10% physiological saline with a mean molecular weight of 40,000 was immediately injected into the tail vein, and 20 minutes later the stomach was excised and fixed in 20% formalin solution from which paraffin blocks were prepared. The specimens were sliced into sections of 30μ and observed under a fluorescent microscopy (Olympus Model FLM). At the same time, H-E stained specimens were used to observe the red blood cell distribution.

RESULTS OF EXPERIMENT

(Ⅰ) Incidence of hemorrhage and erosion

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The findings of hemorrhage and erosion in the controls were noted in 25% after 30 minutes of cold restraint and 88% in both those restrained for 60 and 120 minutes, showing an increase with time.

The corresponding values for V. B_6 deficient diet group were 14%, 44% and 57% while those for the cimetidine group were 0%, 33% and 58% respectively, indicating similar rates.

The findings for the vagotomized group were 0% and 14% each for the latter two (Table 1).

Table 1. Incidence of gastric hemorrhage and erosion after cold restraint

cold restraint (min) / Group	30′	60′	120′
Control	2/8	7/8	7/8
(%)	25	88	88
V. B_6 deficient	1/7	4/9	4/7
(%)	14	44	57
Cimetidine administered	0/12	4/12	7/12
(%)	0	33	58
Vagotomized	0/7	1/7	1/7
(%)	0	14	14

Thus, the rates of both hemorrhage and erosion were decreased in the V. B_6 deficient diet, cimetidine and vagotomized groups as compared to the controls.

(Ⅱ) Gastric acid secretion

The pre-cold restraint gastric acid secretion values of the control group was 3.0 ± 0.5 μEq/ml (M±SD) whreas the 30, 60 and 120 minutes cold restraint values wers 1.3 ± 0.3, 1.6 ± 0.3 and 3.4 ± 0.8 μEq/ml respectively. The findings up to 60 minutes were significantly decreased ($p<0.01$), but reverted to the pre-restraint level at 120 minutes.

In the V. B_6 deficient diet group, the pre-test values was 1.7 ± 0.8 μEq/ml, which was lower than the control group value. After restraint for 30, 60 and 120 minutes, the values were 0.7 ± 0.4, 1.0 ± 0.6 and 1.5 ± 1.0 μEq/ml respectively, failing to demonstrate any significant differences.

The cimetidine group had a gastric acid secretion value of 2.7 ± 0.7 μEq/ml prior to administration of cimetidine, which decreased significantly to 1.1 ± 0.6 μEq/ml ($p<0.01$) after injection. Cold restraint test showed values of 0.7 ± 0.6, 0.7 ± 0.4 and 3.1 ± 0.7 μEq/ml at 30, 60 and 120 minuts respectively, indicating that the values remain low up to 60 minutes.

In the vagotomized group, the pre-test value was 3.6 ± 0.9 μEq/ml which was slightly higher than the control group value, but the test values after 30, 60 and 120 minutes were 1.0 ± 0.4, 0.6 ± 0.5 and 1.3 ± 0.5 μEq/ml which were all lower than those of the control group. The high pre-test value in the vagotomized group is considered to be due to the delay in the excretion of the stomach contents because of inadequate pyloroplasty (Table 2).

(Ⅲ) Histamine content in gastric mucosa

The pre-test gastric mucosal histamine content of the controls was 8.4 ± 1.1 μg/g (M±SD), while after 30, 60 and 120 minutes of cold restraint, it was 4.1 ± 1.5, 8.3 ± 1.2 and 11.9 ± 2.2 μg/g. A significant decrease ($p<0.01$) was noted at 30 minutes after which it incerased.

In the V. B_6 deficient diet group the pre-test value was 2.9 ± 0.6 μg/g which was 1/3 that of the control group. After restraint for 30, 60 and 120 minutes, the values became 3.1 ± 0.5, 2.6 ± 0.5 and 2.4 ± 0.7 μg/g respectively,

Table 2. Gastric acid concetraiton after cold restraint

cold restraint (min)	acid concentration (μEq/ml) 0′	30′	60′	120′
Control<n=4>	3.0±0.5	1.3±0.3*	1.6±0.3*	3.4±0.8
V. B_6 deficient<n=4>	1.7±0.8	0.7±0.4*	1.0±0.6*	1.5±1.0
Cimetidine administered<n=4>	1.1±0.6	0.7±0.6*	0.7±0.4*	3.1±0.7
Vagotomized<n=4>	3.6±0.9	1.0±0.4*	0.6±0.5*	1.3±0.5

*$p<0.01$ (M±SD)

* Significance of the difference between means of the pre-test value and restrained value within each study group.

Table 3. Gastric mucosal histamine content after cold restraint

cold restraint (min)	mucosal histamin content (μg/g) 0′	30′	60′	120′
Control<n=6>	8.4±1.1	4.1±1.5*	8.3±1.2	11.9±2.2
V. B_6 deficient<n=6>	2.9±0.6	3.1±0.5	2.6±0.5	2.4±0.7
Cimetidne administered<n=6>	13.3±2.3	9.1±1.6*	8.8±2.3*	9.6±2.0
Vagotomized<n=6>	18.2±2.2	18.8±1.6	17.6±3.1	14.7±1.9*

*p<0.01 (M±SD)

* Significance of the difference between means of the pre-test value and restrained value within each study group.

failing to demonstrate any significant differences.

The pre-test value for the cimetidine group was 13.3±2.3 μg/g while after restraint for 30, 60 and 120 minutes, the values were 9.1± 1.6, 8.8±2.3 and 9.6±2.0 μg/g respectively, with the values up to 60 minutes being significantly decreased ($p<0.01$).

The vagotomized group had a pre-test value of 18.2±2.2 μg/g which was approximately 2-fold greater than that of the controls. After 30, 60 and 120 minutes of restraint, the values were 18.8±1.6, 17.6±3.1 and 14.7±1.9 μg/g respectively, with the value for 120 minutes being significantly decreased ($p<0.01$) (Table 3).

(Ⅳ) Microvasculature ano red blood cell distribution in the gastric mucosa

The findings of the microvasculature and red blood cell distribution in the controls after cold restraint for 60 minutes were used for comparative study because of the high incidence of ulcer in this group.

Figs. la and b show the microvasculature and red blood cell distribution in the gastric mucosa of normal rats. The mucosal capillaries which run tortuously from the connecting arterioles of the submucosal layer to the capillaries of the mucosal surface and collecting venules are clearly visualized in Fig. la. A few red blood cells can be seen only in the capillaries of the mucosal surface. (Fig. 1b)

Figs. 2a～c show findings after a single venous injection of histamine 5 mg/kg followed by administration of FITC-dextran. Microvasculature can not be visualized in Fig. 2a and only erosion can be seen. Neumerous red blood cells can be observed throughout the vasculature with rouleau formation of red blood cells in some areas. (Figs. 2b, 2c)

Findings of the control group are show in Figs. 3a, b. Only a few capillaries of the mucosal surface can be vaguely visualized in Fig. 3a, but the mucosal capillaris and collecting venules can not be seen. Findings indicating bleeding into the stomach are observed. Neumerous red blood cells can be seen in the mucosal capillaries, capillaries of the mucosal surface and collecting venules, which resemble the findings observed following the administration of histamine.

Figs. 4a, b show findings of the V. B_6 deficient diet group, Figs. 5a, b indicate the cimetidine group and Figs. 6a, b represent the vagotomized group. The microvasculature of these 3 groups were better visualized than the controls, but the red blood cell distribution was less, being observed only in the capillaries of the mucosal surface and collecting venules.

DISCUSSION

Selye[9,10] in 1948 reported that ulcers develop in the digestive tract as a phenomenon of alarm reaction of the body to stress, and attempted to induce stress ulcers in labobatory animals. Ever since various experimental models have been devised for the purpose of elucidating the developmental mechanism of stress ulcers.

The cold restraint model[11] used by the authors is a method that definitely produces acute gastric ulcer in a short period of time. It is also a useful model to study the effects of drugs which are rapidly metabolized. Gastrostomy (chronic gastric fistula) and FITC-dextran method[12] were employed for the purpose of observing the physical reactions to stress under as close to physiological condi-

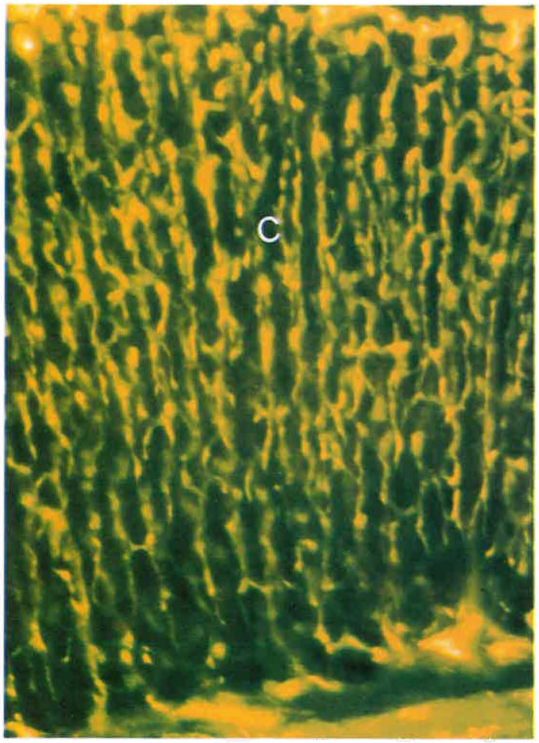

Fig. 1a. Microangiograph in the gastric mucosa of normal rats. The capillary systems are clearly visualized. Mucosal capillary (C), ×50

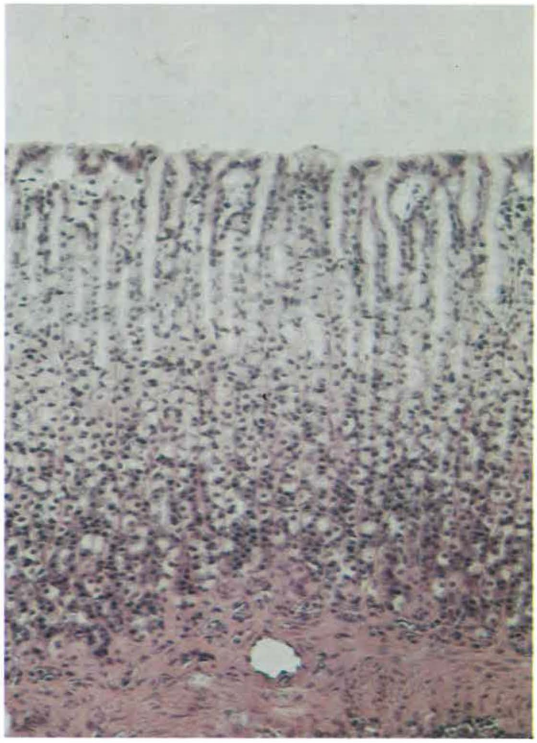

Fig. 1b. Section of normal rats. A few red bool cells can be seen only in the capillaries of the mucosal surface. HE, ×50

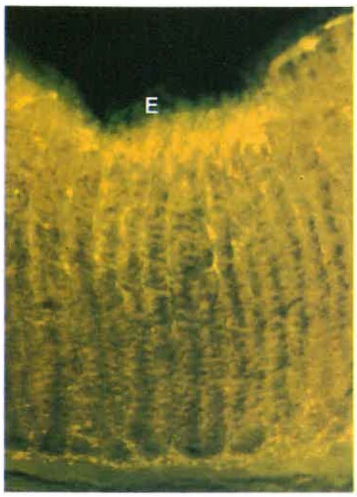

Fig. 2a. Microangiograph of histamine 5 mg/kg administered rats. The capillary can not be visualized. Only erosion can be seen. Erosion (E), ×50

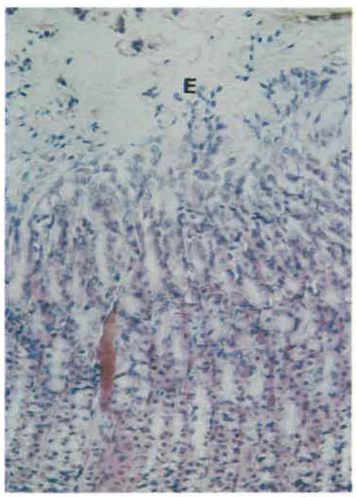

Fig. 2b. Section of histamine 5 mg/kg administered rats. Dilatation of capillaries and red blood cell stasis can be seen. Erosion (E), HE, ×100

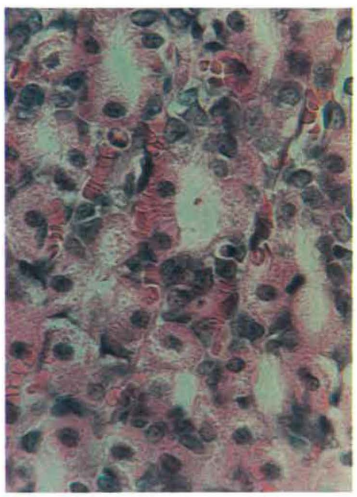

Fig. 2c. Higher magnification of an area of Fig. 2b. The capillaries with rouleau formation can be seen. ×200

Fig. 3a. Microangiograph of the control group after cold restraint for 60 minutes. Only a few capillaries of the mucosal surface can be vaguely visualized. The bleeding into the stomach are observed. ×50

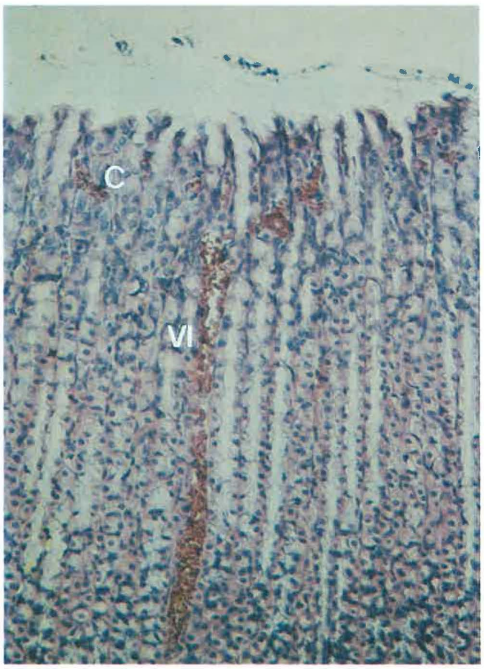

Fig. 3b. Section of the control group after cold restraint for 60 minutes. Neumerous red blood cells can be seen in the capillaries of the mucosal surface and collecting venules.
Mucosal capillary (C), Collecting venules (Vl), HE, ×50

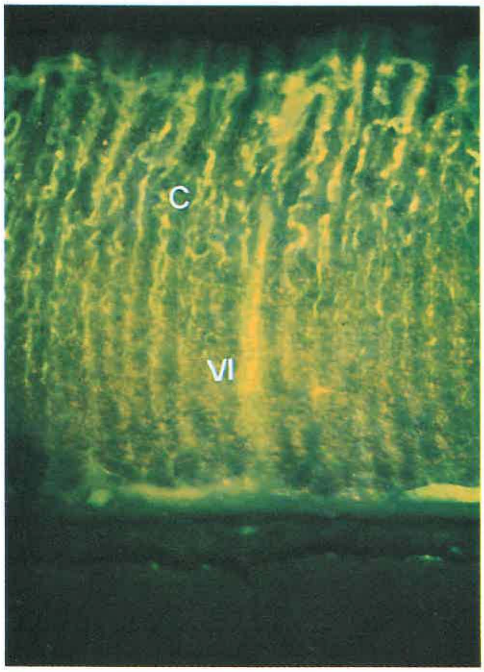

Fig. 4a. Microangiograph of the V. B_6 deficient diet group after cold restraint for 60 minutes. Mucosal capillary (C), Collecting venules (Vl), ×50

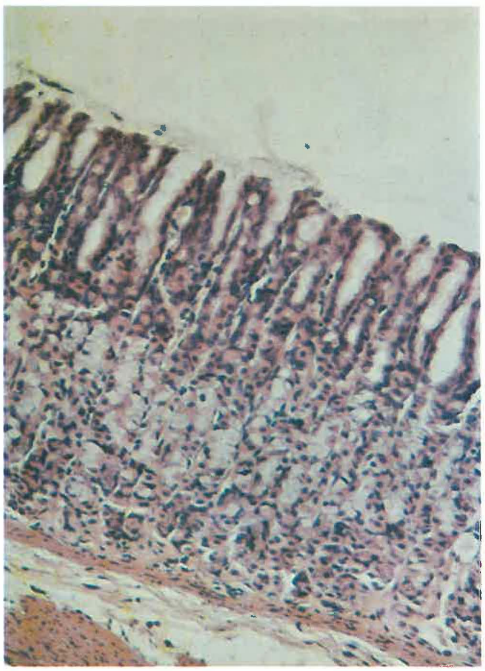

Fig. 4b. Section of the V. B_6 deficient diet group after cold restraint for 60 minutes. HE, ×50

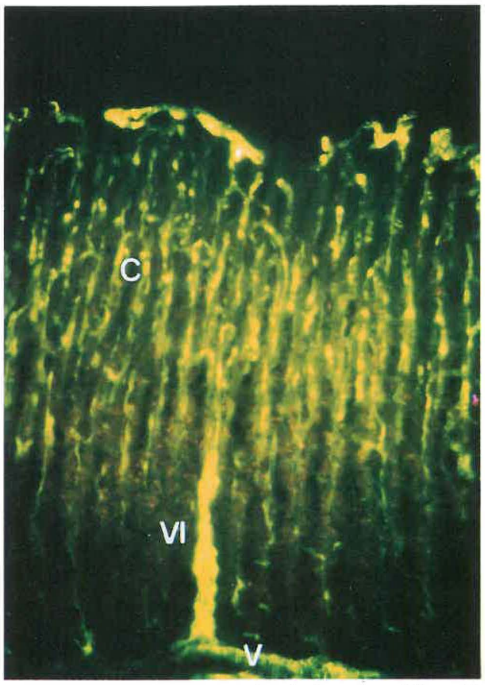

Fig. 5a. Microangiograph of the cimetidine 48 mg/kg administered group after cold restraint for 60 minutes.
Mucosal capillary (C), Collecting venules (Vl), Collecting vein (V), ×50

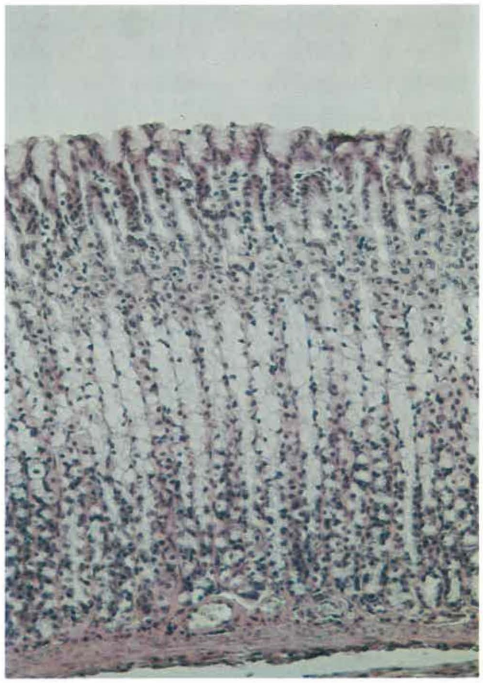

Fig. 5b. Section of the cimetidine 48 mg/kg administered group after cold restraint for 60 minutes. HE, ×50

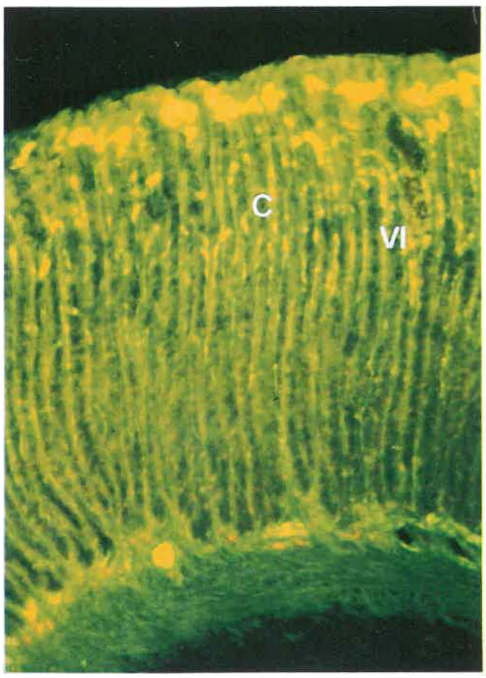

Fig. 6a. Microangiograph of the vagotomized group after cold restraint for 60 minutes. Mucosal capillary (C), Collecting venules (Vl), ×50

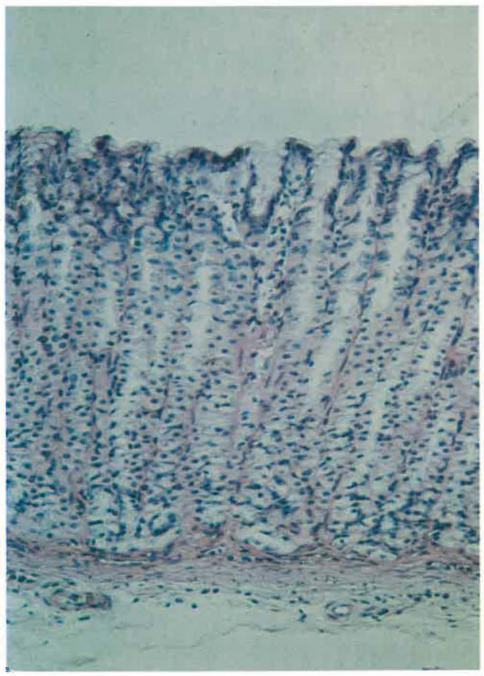

Fig. 6b. Section of the vagotomized group after cold restraint for 60 minutes. HE, ×50

tions as possible.

The 1) gastric acid secretion, 2) histamine content in gastric mucosa and 3) microvasculature and red blood cell distribution in gastric mucosa will be reviewed hereunder.

1) Gastric acid secretion

Reports on gastric acid secretion under stress vary by the experimental model employed. Brodie[13] and Klein et al.[14] have reported noticing decrease in gastric fluid and increase in acid concentration in restrained models, while Singh et al.[15] claim there is an increase in both gastric fluid and acid concentration when a rocking model was used. Menguy[16] subjected pylorus ligated rats to restaint, while Brodie[17] used a restraint plus cold model, and the findings in both cases indicated decreases in both gastric fluid and acid concentration.

Mersereau et al.[18] in their study of the relationship of gastric acid and ulcers, observed the relation between intragastric H^+ ion concentration and ulcerogenesis and reported that ulcers do not develop in normal gastric mucosa even when choloric acid is introduced into the stomach, but they are frequently found when the mucosa has been injuried or in areas which come into contact with the reflex of bile. Thus, they point out that the initial ulcerous change were atributable more to changes in the mucosa rather than due to acid.

The findings obtained by the authors after the respective cold restraint periodes showed that all three groups had lower values than the controls. Further, the four groups showed similar patterns with values decreasing among those restrained up to 60 minutes, but demonstrating increase at 120 minutes. These findings suggest that factors other than acid are involved in causing hemorrhage and erosion in the cold restraint rats. Brodie et al.[17] report that the gastric lesion they noted in their model which had develop reduced acid secretion after being subjected to restraint plus cold, was hemorrhage only without any erosion. It is presumed that rather than being the factor directly responsible for hemorrhage and erosion, acid more likely promotes the hemorrhage and erosion which has developed.

2) Histamine content of gastric mucosa

McIntosh[19], Brodie[20], Kahlson[21], Shore[22], Kim[23] and others report that histamine in the gastric mucosa is released by the vagal excitation, while others claim humoral factor such as adrenalin (Staub[24]) and corticosteroid (Singh[15] and Guth et al.[25]) are involved. Further, Shey et al.[26] report that they observed the effects of the vagus and adrenal gland upon gastric acid secretion, and noted that the effects of the adrenal gland appeared about two hours after the nerve effects.

When considering the results obtaind by the authors in light of the above findings, it is felt the decrease in histamine value in the gastric mucosa after 30 minutes of cold restraint is due to its release induced by the vagal excitation. No histamine release up to 60 minutes is noted in the vagotomized group, but that found at 120 minutes is presumed to be due to humoral factors. On the other hand, decrease in histamine synthesis does not cause release of histamine in the gastric mucosa.

Lorenz et al.[27] have published a similar report regarding the high histamine value in animals subjected to vagotomy and pyloroplasty.

It is known that histamine synthesis is promoted by gastrin.[28,29] The authors noticed an increase in the serum gastrin level following vagotomy and pyloroplasty, and it is presumed the high histamine value in the vagotomized group is due to elevation in the serum gastrin level.

The above findings suggest that the development of stress ulcers is due more to the histamine released rather than the local mucosal histamine content.

3) Microvasculature and red blood cell distribution in gastric mucosa

In 1853, Virchow[30] advocated the theory that blood vessels were responsible for the production of ulcers, and subsequently many reports have been published on the relationship of ulcers and microcirculation in the gastric mucosa. It is generally considered that circulatory insufficiency in the gastric mucosa causes hypoxia and results in devitalization of the mucosa.

There are two conflicting opinions on the cause of hypoxia, that is the ischemia theory and the capillary stasis theory due to plethora. Reports supporting the ischemia theory include capillary spasmus caused by acid[31], contraction of the arterioles due to sympathetic stimulation[32], compression of the capillaries due to gastric contraction caused by vagal stimula-

tion[33] and others. While reports favoring the plethora theory include dilation of the arterioles and closure of the A-V shunt[34] by histamine, vascular engorgiment caused by vagal stimulation[35),36] and others.

Review of the findings obtained by the authors indicates that persistent stress causes continuous large volume release of histamine resulting in dilation of the submucosal arterioles and closure of A-V shunt which causes the flow of blood into the gastric mucosa to largely exceed that produced by physiological reaction resulting in a relative narrowing of the veins, and its enhanced capillary permeability acts synergetically causing stasis of the microvasculature resulting in hypoxia of the local gastric mucosa. On the other hand, it is considered that inhibition of histamine release prevents the development of stasis in the local gastric mucosa and will maintain good microcirculation.

The gastric acid secretion inhibiting effect of histamine H_2 receptor antagonist is well known. During recent years, it has been found that there are not only H_1 receptors in the vascular wall, but also H_2 receptors as well[37], thus attentions is being focussed on the role of the H_2 receptor antagonist.

Guth et al.[38] have pointed out ths presence of the H_1 and H_2 receptors in the arterioles of rat gastric mucosa, and reported that H_1 and H_2 receptors when stimulated by histamine cause dilation of the arterioles. When the findings of the authors are considered in the light of these findings, it is felt that the arteriole dilating action of histamine was inhibited by the administration of cimetidine which in turn inhibited increase in mucosal blood flow, and thus mucosal microcirculation was retained which served to prevent ulceration.

CONCLUSION

Studies with emphasis on histamine were performed on cold restraint rats for the purpose of elucidating the mechanism of ulcerogenesis due to stress and the couse of ulcer development is assumed to be as outlined in Fig. 7.

The histamine released from the gastric mucosa of cold restraint rats by the vagus dose not directly affect gastric acid secretion, but rather affects the capillaries of the mucosa causing circulatory disturbance and devitalization of the mucosa, resulting in hemorrhage and erosion. Gastric acid acts upon the sources of bleeding and erosion, and aggravates them.

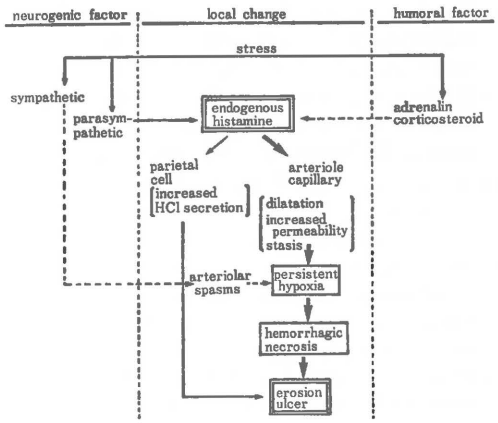

Fig. 7. The role of histamine in stress ulcer decer development

On the other hand, vagotomy inhibits the release of histamine, and cimetidine blocks the effects of histamine on capillaries of the mucosa. Thus, they assume the role of protecting the capillary dynamics which, it is considered, prevented the development of ulcer.

ACKNOWLEDGMENT

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