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European Journal of Pharmacology 275 (1995) 179–184

ejp

Histamine chloramines have a persistent stimulating effect on histamine H_2 receptors and gastric acid secretion

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Received 4 August 1994; revised 13 December 1994; accepted 16 December 1994

Abstract

Histamine plays an important role in the control of gastric acid secretion. Recently, chlorinated derivatives of histamine have been identified as having multiple effects on the intestinal tract. The aim of this study was to investigate the role of histamine chloramines on gastric acid secretion. We compared the effects of histamine and histamine chloramines on the histamine H_2 receptors in vitro using guinea pigs and on gastric acid secretion in rats. With respect to the effects on histamine H_2 receptors, histamine monochloramine showed agonist effects similar to those seen with histamine, but the agonist effects of histamine dichloramine were about half those of histamine. Unlike histamine effects, the histamine H_2 receptor agonist effects of histamine monochloramine and histamine dichloramine did not disappear after repeated washout. With respect to the stimulation of gastric acid secretion in vivo, histamine monochloramine was similar to histamine, while the effect of histamine dichloramine was 42.2–52.7% of that of histamine. The recovery time to the basal secretory level after completion of stimulation by histamine chloramines was significantly prolonged compared with histamine. These results suggest that histamine chloramines, which bind strongly with histamine H_2 receptors, may delay the termination of gastric acid secretion and increase the burden on the gastric and duodenal mucosa.

Keywords: Histamine; *Helicobacter pylori*; Histamine chloramine; Gastric acid secretion

1. Introduction

Among the pathophysiological conditions which characterize duodenal ulcer, there is increased acid secretion in patients with duodenal ulcer as a group both basally and in response to a variety of stimuli such as histamine and gastrin, as compared to normal subjects (Malagelada et al., 1977; Bodemar et al., 1978; Feldman and Richardson, 1986).

On the other hand, the presence of the gram-negative bacterium *Helicobacter pylori* (*H. pylori*) in the human stomach is recognized as having an etiologic role in duodenal ulcer (Warren, 1983; Marshall and Warren, 1984; Goodwin et al., 1986; Levi et al., 1989; Paull and Yardley, 1989; Graham, 1991). It is now well established that up to 100% of duodenal ulcer patients are infected with the bacterium and have inflammation of the gastric mucosa in both the antrum and corpus. The presence of *H. pylori* is associated with a mucosal inflammatory reaction that consists of a large number of polymorphonuclear and mononuclear inflammatory cells (Warren, 1983; Marshall and Warren, 1984; Goodwin et al., 1986; Paull and Yardley, 1989).

Histamine plays an important role in the control of gastric acid secretion as a paracrine mediator. Patients with duodenal ulcer have significantly lower concentrations of gastric mucosal histamine than control subjects and this has been suggested to be related to their state of high mobilization of endogenous mucosal histamine with depletion of its stores (Troidl et al., 1976; Shaff and Beaven, 1979; Lönroth et al., 1990b; Queiroz et al., 1991).

Recently, chlorinated derivatives of histamine have been identified as having multiple effects on the intestinal tract (Miller et al., 1991, 1992). Polymorphonu-

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Elsevier Science B.V.
SSDI 0014-2999(94)00773-X

clear leucocytes play a critical role in the disruption of the epithelial barrier by releasing oxidants, such as hydrogen peroxide and hypochlorous acid (Welsh et al., 1985; Von Ritter et al., 1989; Wallace and Keenan, 1990; Nash et al., 1987,1988). Chlorinated derivatives of histamine are produced by chemical reaction with hypochlorous acid that is released by polymorphonuclear leukocytes. Because neutrophils invade an area rich in mast cells, neutrophil-derived hypochlorous acid can interact with histamine to generate histamine chloramine (Wright and Low, 1989; Miller et al., 1992). Histamine chloramine retains both histamine agonist properties and an oxidizing potential.

Hyperacidity and *H. pylori* infection in the stomach are important etiological factors in duodenal ulcer disease. However, the interrelationship between mucosal inflammation and control of gastric acid secretion is unclear. We studied the effects of histamine chloramines (histamine monochloramine and histamine dichloramine) on the histamine H_1 and H_2 receptors and gastric acid secretion to investigate a possible role of histamine chloramines in gastric acid secretion.

2. Materials and methods

2.1. Animals

Male Hartley guinea pigs weighing 332–368 g were acclimatized in the animal room under temperature conditions of 22 ± 2°C, humidity 55 ± 15%, and illumination time of 8:00 a.m. to 8:00 p.m. before use. Male Sprague Dawley rats weighing 250–300 g were deprived of food but allowed free access to tap water for 12 h prior to the experiments.

2.2. Chemicals

The following chemicals were purchased from the sources indicated: histamine dihydrochloride (Wako Pure Pharmaceutical Co., Kyoto), sodium hypochlorite (Wako Pure Pharmaceutical Co., Kyoto).

2.3. Preparation of histamine chloramines

Histamine chloramines were prepared according to the methods described by Miller et al. (1992) and Wright and Low (1989). Briefly, histamine monochloramine (HisCl) was prepared by a 20-min incubation with histamine dihydrochloride 5 mmol/l and sodium hypochlorite 5 mmol/l in 0.05 mol/l phosphate-buffered solution (pH 7.0) at 37°C. Histamine dichloramine ($HisCl_2$) was prepared by a 20-min incubation with histamine 5 mmol/l and sodium hypochlorite 10 mmol/l in 0.05 mol/l phosphate-buffered solution (pH 5.0) at 37°C. Production of histamine chloramines was confirmed by spectrophotometry (UV-260, Shimazu Factory Co.). Absorbance was measured continuously at 240–360 nm of the wavelength, following the method of Wright and Low (1989). The absorbance curve of HisCl (about 250 nm) produced by the incubation with sodium hypochlorite (maximum absorbance at 292 nm) and histamine at 37°C and pH 7.0, and that of $HisCl_2$ (300 nm) produced by incubation with sodium hypochlorite and histamine were almost identical to those reported by Wright and Low. Thus, the results were taken to show that HisCl and $HisCl_2$ had been produced (Fig. 1). Because HisCl and $HisCl_2$ decomposed when they were left at room temperature, they were stored on ice, which enabled these chloramines to be preserved for about 6 h.

2.4. Effects of histamine and histamine chloramines on histamine H_1 receptors

The ileum from a male guinea pig was obtained and a 1-cm-long specimen was suspended in an organ bath (32°C, 30 ml) filled with Tyrode solution (components: NaCl, 137.9; KCl, 2.7; $CaCl_2$, 1.8; $MgCl_2$, 0.5; NaH_2PO_4, 1.1; $NaHCO_3$, 11.9; glucose, 5.6 mmol/l) in

Fig. 1. Typical absorbance spectra chart of histamine monochloramine and histamine dichloramine. (A). (a) Sodium hypochlorite (5 mmol/l); (b) histamine (5 mmol/l) + sodium hypochlorite (5 mmol/l) incubated in 0.05 mol/l phosphate buffer (pH 7.0) for 20 min at 37°C. (B). (a) Sodium hypochlorite (10 mmol/l); (b) histamine (5 mmol/l) + sodium hypochlorite (10 mmol/l) incubated in 0.05 mol/l phosphate buffer (pH 5.0) for 20 min at 37°C.

which a mixed gas (95% O_2 and 5% CO_2) was flowing. The contraction was measured isotonically under a 1-g load by means of an isotonic transducer (TD-112 S, Nihon Koden and UT-202, Kishimoto Medical). The experiment was started after confirmation that the specimen was sufficiently stable. The pD2 was obtained from the concentration-reaction curve resulting from the reaction on cumulative application of histamine, HisCl and $HisCl_2$. Six trials were carried out for each chemical, and the results were expressed as the mean level ± standard error (S.E.).

2.5. Effects of histamine and histamine chloramines on histamine H_2 receptors

The right atrium obtained from a guinea pig was kept at 32°C, and was suspended in an organ bath (30 ml) filled with Krebs-Henseleit solution (components NaCl, 118; KCl, 4.7; $CaCl_2$, 2.5; NaH_2PO_4, 1.2; $NaHCO_3$, 25.0; $MgSO_4$, 1.2; glucose, 10 mmol/l) in which a mixed gas (95% O_2 and 5% CO_2) was flowing. The contraction was measured isotonically under a 1-g load by means of an isometric transducer (TB-651T, Nihon Koden). Pulsation was measured by immediate cardiography (AT-601G, Nihon Koden). The experiment was started after confirmation that the specimen was sufficiently stable. The pD_2 was obtained from the concentration-reaction curve resulting from the reaction on cumulative application of histamine, HisCl and $HisCl_2$. Six trials were carried out for each chemical, and the results were expressed as the mean level ± S.E.

2.6. Effect of histamine and histamine chloramines on gastric acid secretion in vivo

Using male SD rats weighing 250–300 g fasted for 24 h, the stomach was placed in an ex-vivo chamber under urethane anesthesia (1.0 g/kg, i.m.) (Mersereau and Hinchey, 1973). For measurement of acid secretory values, 2 ml of physiological saline solution was placed into the chamber, and replaced every 15 min. Acid secretion was titrated with 0.01 N NaOH, and the acid secretory value per 15 min was calculated. After the basal secretory value was measured for 1 h, histamine, HisCl or $HisCl_2$ (10, 20 μmol/kg per h) was infused via the femoral vein. The infusion was terminated after 1 h, and the acid secretory value was then measured for 2 h after completion of stimulation.

2.7. Statistical analysis

The data are presented as the means ± S.E. (S.D.) per group. Statistical analysis was performed using Student's t-test, and $P < 0.05$ was regarded as significant.

3. Results

3.1. Effects of histamine and histamine chloramines on histamine H_1 receptors

The effects of histamine and histamine chloramines were investigated using the contraction of an isolated guinea pig ileum as an index. Similar concentration-reaction curves for histamine, HisCl and $HisCl_2$ were obtained up to 3×10^{-5} mol/l, and no significant difference was seen among the three chemicals (Fig. 2). The respective pD_2s of histamine, HisCl and $HisCl_2$ were 5.71 ± 0.12, 5.75 ± 0.08 and 5.73 ± 0.10 (means ± S.E.), which were similar. The stimulatory effects of histamine, HisCl and $HisCl_2$ disappeared promptly after they were removed from the bath.

3.2. Effects of histamine and histamine chloramines on histamine H_2 receptors

The effects were investigated using the heart rate of an isolated guinea pig right atrium as an index. The concentration-reaction curves of histamine and HisCl were similar up to 10^{-7}–3×10^{-5} mol/l. On the other hand, the curve for $HisCl_2$ was shifted slightly to the right in comparison with that of histamine (Fig. 3). The pD_2 of histamine, HisCl and $HisCl_2$ were 5.93 ± 0.04, 5.86 ± 0.07 and 5.62 ± 0.12 (mean ± S.E.), respectively. The data show that the stimulatory effects of histamine monochloramine on histamine H_2 receptors did not differ greatly from those of histamine, while the effects of histamine dichloramine were shown to be reduced to half those of histamine. However, a notable difference was seen after the washout of the chemicals in this experiment. After measurement of the maximum reaction with each chemical, the chemical was washed

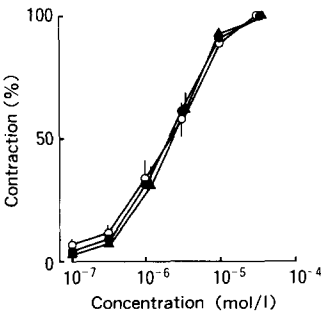

Fig. 2. Concentration-response curves for histamine and histamine chloramines with an isolated guinea pig ileum. The potency of histamine and histamine chloramines on the histamine H_1 receptors was investigated using the contraction of an isolated guinea pig ileum as an index and the reaction to 3×10^{-5} mol/l is expressed as 100%. Each point represents the mean ± S.E. of six preparations. Each compound was added to the bath cumulatively. No difference was seen among histamine, histamine monochloramine, and histamine dichloramine. (○): histamine, (●): histamine monochloramine, (▲): histamine dichloramine.

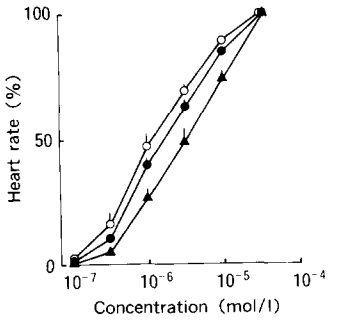

Fig. 3. Concentration-response curves for histamine and histamine chloramines with an isolated guinea pig right atrium. The potency was investigated with the heart rate of an isolated guinea pig right atrium as an index and the reaction to 3×10^{-5} mol/l is expressed as 100%. Each point represents the mean ± S.E. of six preparations. Each compound was added to the bath cumulatively. The effects of histamine monochloramine (●) on histamine H_2 receptors did not differ greatly from that of histamine (○), while the effects of histamine dichloramine (▲) were shown to be reduced compared to those of histamine.

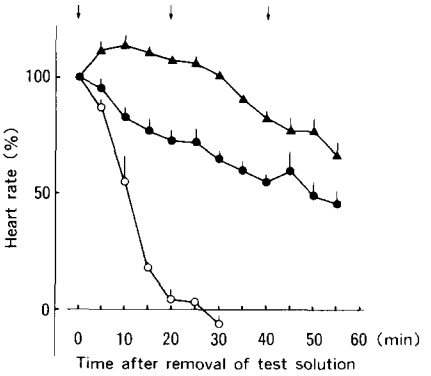

Fig. 4. Positive chronotropic action of histamine and histamine chloramines after the removal of test solution in an isolated guinea pig right atrium. The washout was repeated every 20 min after the maximal cumulative dose-response. When recovery of the heart rate with the passage of time was observed, that with histamine recovered to its value before treatment in 20 min, whereas the rates with HisCl and $HisCl_2$ did not recover to the rates recorded before treatment, even at 50 min. Each point represents the mean ± S.E. of six preparations. (○): histamine, (●): histamine monochloramine, (▲): histamine dichloramine, ↓: wash.

repeatedly at intervals of 15–20 min (exchange of nutrient solution twice for each washing). When recovery of the heart rate with time was observed, histamine was easily washed out and the heart rate recovered completely to the before treatment rate in 20 min. On the other hand, the stimulatory effects of HisCl and $HisCl_2$ did not disappear promptly after the drugs were removed from the bath, which indicated strong binding to the receptors (Fig. 4).

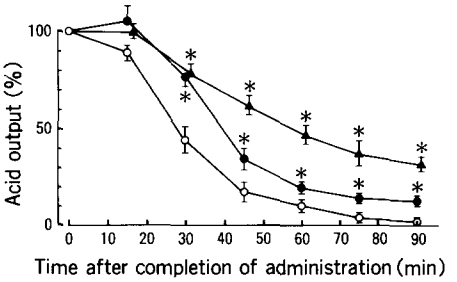

Fig. 5. Comparison of the effects of histamine, HisCl and $HisCl_2$ on gastric acid secretion after completion of the administration of these agents. Termination of the gastric acid secretion after completion of the stimulation by HisCl and $HisCl_2$ (10 μmol/kg per h) was delayed significantly compared to that of histamine (10 μmol/kg per h). Each value indicates acid output over 15 min and is expressed as a percentage of the amount of acid which was secreted during the 15 min prior to completion of stimulation by these agents. (○) Histamine, (●): histamine monochloramine, (▲): histamine dichloramine. Each point represents the mean ± S.E. for five rats. * Significant compared with histamine, $P < 0.05$.

3.3. Effects of histamine and histamine chloramines on gastric acid secretion in vivo

Continuous intravenous infusion of histamine, HisCl or $HisCl_2$ (10, 20 μmol/kg per h) for 1 h caused an increase in gastric acid secretion. There was no significant difference in acid output between histamine and HisCl, but the acid output stimulated by $HisCl_2$ was 42.2–52.7% of that of histamine ($P < 0.01$) (Table 1). After completion of a 1-h stimulation by histamine, the acid secretion rapidly returned to the basal level. On the other hand, the acid secretion stimulated by HisCl or $HisCl_2$ (10, 20 μmol/kg per h) persisted after completion of the stimulation, and took a longer time to return to the basal level in comparison with that of histamine (Fig. 5).

4. Discussion

Histamine plays an important role in the control of gastric acid secretion, as a paracrine mediator. On the

Table 1
Effects of histamine, HisCl and $HisCl_2$ on gastric acid secretion in rats

Stimulant	10 μmol/kg per h			20 μmol/kg per h		
	Basal value	During stimulation	Peak acid output	Basal value	During stimulation	Peak acid output
Histamine	16.6 ± 3.8	65.1 ± 6.6	98.1 ± 5.7	14.2 ± 11.2	68.3 ± 12.1	113.5 ± 23.3
HisCl	17.8 ± 6.4	57.5 ± 8.8	93.3 ± 9.6	11.4 ± 7.6	60.3 ± 11.9	97.5 ± 12.5
$HisCl_2$	12.3 ± 5.5	27.5 ± 7.3	48.1 ± 9.7	9.9 ± 4.4	35.5 ± 10.6	59.8 ± 14.0

HisCl, histamine monochloramine; $HisCl_2$, histamine dichloramine; means ± S.D., μEq/h, $n = 5$.

other hand, histamine has been identified as a potential substrate for chloramine formation (Wright and Low, 1989; Miller et al., 1992). Chlorinated derivatives of histamine have been identified as having several effects in the intestinal tract, such as epithelial permeability and epithelial cell cytotoxity (Miller et al., 1991, 1992). Histamine chloramine retains both histamine agonist properties and an oxidizing potential. However, the effects of histamine chloramines on histamine H_1 and H_2 receptors and gastric acid secretion have not been investigated.

With respect to the agonist effects of histamine, HisCl and $HisCl_2$ on histamine H_1 and H_2 receptors, the three chemicals showed similar effects on histamine H_1 receptors. However, while the effects of histamine and HisCl on histamine H_2 receptors were similar, those of $HisCl_2$ was about half those of histamine. Histamine promptly lost its effects on histamine H_2 receptors after undergoing washout, whereas HisCl and $HisCl_2$ did not lose their effects even at 50 min. With respect to the acid secretion in vivo, we were able to demonstrate that acid secretion stimulated by HisCl and $HisCl_2$ persisted significantly after the stimulation completion and took a longer time to return to the base level in comparison to that of histamine. For the effective regulation of acid secretion, rapid removal of histamine is essential to allow the immediate termination of the stimulatory action when the signal for histamine release is discontinued. Gastric mucosa has the capacity of rapid elimination of histamine, leading to immediate termination of stimulation (Loiselle and Wollin, 1993). The present results suggest that termination of the acid secretory response may be impaired in the presence of histamine chloramines. This would lead to an exaggerated acid secretory response and an increase in the burden on the gastric and duodenal mucosa. There are data suggesting that duodenal ulcer patients, as a group, have a persisting acid secretory reaction after food intake and lower duodenal pH for a longer period than control subjects, both in the fasting state and in response to food (Malagelada et al., 1977; Bodemar et al., 1978; Feldman and Richardson, 1986).

It is now well established that up to 100% of duodenal ulcer patients are infected with *H. pylori* and have inflammation of the gastric mucosa in both the antrum and corpus. The presence of *H. pylori* is associated with the mucosal inflammatory reaction that consists of large number of polymorphonuclear and mononuclear inflammatory cells (Paull and Yardley, 1989). Hypochlorous acid is released by neutorophilic leukocytes and reacts with first class amines such as histamine to yield histamine chloramines (Weiss et al., 1982; Test et al., 1984; Klebanoff, 1988; Wright and Low, 1989).

Since it has been indicated that *H. pylori* activates neutrophils (Mooney et al., 1991) and that the histamine level in the gastric mucosa of *H. pylori*-positive persons is low (Troidl et al., 1976; Queiroz et al., 1991), histamine chloramines may be produced in the stomach of patients with *H. pylori* infection. Histamine has long been recognized as a gastric secretagogue, and since the introduction of histamine H_2 receptor antagonist, its physiological role in regulating gastric secretion is accepted (Ash and Schild, 1966; Black et al., 1972). In the human, gastric mucosal histamine is stored in the enterochromaffin-like cells (ECL cells), which are present in the both antrum and corpus and located close to or adjacent to parietal cells (Lönroth et al., 1990a). Activated neutrophils can release hypochlorous acid in the range of 80–200 μmol/l (Grisham et al., 1984) and the interaction between hypochlorous acid and primary amines is extremely rapid and probably only limited by diffusion, i.e., molecular contact. Thus, in inflamed lamina propria where ECL cells and granulocytes are in juxtaposition, histamine chloramine formation is a possibility. However, because hypochlorous acid and chloramines are highly labile, it is not possible to measure their concentrations in the tissues.

In these experiments, it became clear that histamine chloramines act on histamine H_2 receptors. Therefore, in the presence of these chloramines, they should have some deleterious influence on the control of gastric acid secretion. However, the results of studies on the effect of *H. pylori* infection on human gastric acid secretion are controversial (Rademaker and Hunt, 1991). Our results suggest that clinical studies on the termination of gastric acid secretion before and after eradication of the organism and healing of inflammatory changes of the mucosa should be performed.

Acknowledgements

Supported by a grant from the S. Hujii Medical Foundation.

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