Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmacology 481 (2003) 233–240
www.elsevier.com/locate/ejphar

Direct effects of proton pump inhibitors on histamine release from rat enterochromaffin-like cells

Tomoyuki Yokota[a], Hidetaka Matsui[a], Bunzo Matsuura[a], Kazutaka Maeyama[b], Morikazu Onji[a,*]

[a] *Third Department of Internal Medicine, Ehime University School of Medicine, Shigenobu-cho, Onsen-gun, Ehime-ken, Japan*
[b] *Department of Pharmacology, Ehime University School of Medicine, Shigenobu-cho, Onsen-gun, Ehime-ken, Japan*

Received 9 May 2003; received in revised form 4 September 2003; accepted 5 September 2003

Abstract

Enterochromaffin-like (ECL) cells play a central role in the regulation of gastric acid secretion. Previous studies have shown that proton pump inhibitors accelerate histamine release from ECL cells through the effects of gastrin. However, direct effects of proton pump inhibitors on ECL cells have not been demonstrated to date because the indirect effects of gastrin are difficult to suppress. We investigated the direct effects of proton pump inhibitors medication on ECL cells using an elutriation system. ECL cells were stimulated with gastrin or rabeprazole, and histamine release from ECL cells was measured. Rabeprazole increased histamine release through a pathway that differed from that of gastrin. The histamine increase was likely due to an acceleration of vesicular monoamine transporter 2 (VMAT2). Rabeprazole increased histamine release from ECL cells directly via VMAT2, but did not affect the total amount of histamine in the cells. The results suggest that patients receiving proton pump inhibitors for extended periods must be monitored extensively because gastric tumor proliferation may be promoted by increased histamine release from ECL cells.
© 2003 Elsevier B.V. All rights reserved.

Keywords: Enterochromaffin-like cell; Histamine; Proton pump inhibitor

1. Introduction

Histamine H_2 receptor antagonist, which block histamine receptors on parietal cells, have been used to treat disorders such as upper gastrointestinal ulcers and gastroesophageal reflux disease. Proton pump inhibitors, which inhibit an H^+, $-K^+$-ATPase of parietal cells in the stomach and suppress the secretion of gastric acid, have also been used to treat these diseases. Gastrin, acetylcholine, and histamine stimulate gastric acid secretion from parietal cells. Histamine, the primary stimulator in humans and most animals (Hersey and Sachs, 1995), was initially thought to originate in the mast cells of the gastric mucosa. However, recent studies have identified enterochromaffin-like (ECL) cells as the more likely histamine source. ECL cells, which are a type of endocrine cell, play a central role in the regulation of gastric acid secretion (Lindström et al., 2001) and are located in the lower third of the gastric gland of the oxyntic mucosa, near the parietal cells. The ECL cells are 8–10 μm in diameter and have numerous electron-lucent cytoplasmic vesicles and few electron-dense granules (Håkanson et al., 1994b). Histamine, which is stored in the vesicles, is secreted by exocytosis upon stimulation by gastrin released from G-cells and in turn stimulates parietal cells through the paracrine pathway.

Proton pump inhibitors cause hypergastrinemia by eliminating the acid feedback inhibition of gastrin release, which results in ECL cell hyperplasia, dysplasia, and even neoplasia in rats (Chen et al., 1999). It is known that proton pump inhibitors inhibits H^+, K^+-ATPase (P-type ATPase). Moreover, there is a report that suggests proton pump inhibitors inhibit V-type ATPase in osteoclasts (Misunashi et al., 1993). In ECL cells, V-type ATPase also plays a role in proton transport into the secretory vesicles, which contain histamine (Prinz et al., 1999). Accordingly, it is possible that proton pump inhibitors cause not only indirect effects of gastrin but also direct effects to ECL cells.

The aim of the present study was to investigate the direct effects of proton pump inhibitors medication on histamine

* Corresponding author. Tel.: +81-89-960-5308; fax: +81-89-960-5310.
E-mail address: onjimori@m.ehime-u.ac.jp (M. Onji).

0014-2999/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2003.09.011

release from ECL cells using an elutriator system, while eliminating the indirect effects of gastrin.

2. Materials and methods

2.1. Chemicals

Rat gastrin-17 was purchased from Sigma (St. Louis, MO). Matrigel was purchased from Becton Dickinson (Bedford, MA). Reserpine, an inhibitor of vesicular monoamine transporter 2, was purchased from Sigma. Anti-histidine decarboxylase was purchased from Euro Diagnostica (Malmö, Sweden). Sodium rabeprazole was kindly provided by Eisai Pharmaceuticals (Tokyo, Japan). All other chemical reagents were of analytical grade.

2.2. Medium

To study ECL cells, all medium of culture, isolation and secretion was used according to a previous experiment (Lindström and Håkanson, 2001).

2.2.1. Krebs-Ringer-HEPES medium

HEPES (25 mM), pH 7.4, 104 mM NaCl, 5 mM KCl, 1 mM KH_2PO_4, 1.2 mM $MgSO_4$, 2 mM $CaCl_2$, 0.01% soybean trypsin inhibitor, and 0.2% bovine serum albumin.

2.3. Isolation and primary culture of ECL cells

Three male Sprague–Dawley rats (CREA, Japan), weighting 250–300 g each, were kept in a cage and fed ad libitum. ECL cells were purified from the rats using an elutriator system as described in detail in the previous study (Prinz et al., 1993; Lindström et al., 1997). We used a modification of the Lindström method to isolate ECL cells from rat stomach. The stomach was closed at the esophageal-gastric junction and the fundus-antrum border by suturing, everted, and closed further by suturing the fundus-forestomach. This isolated a sac containing the acid-producing section of the stomach. The surface of the sac was rinsed with 0.9% saline and blotted with a KimWipe™. Subsequently, 3–5 ml of 1.0 mg ml^{-1} pronase was injected into the interior of the stomach sacs by syringe, and the sacs were incubated for 30 min in medium A at 37 °C under oxygenated conditions (95% O_2, 5% CO_2). Medium A was discarded after 30 min and the sacs were then incubated in medium B for 10 min at 37 °C. The sacs were again incubated in medium A for 20 min and then in medium B for 10 min with magnetic stirring. This was followed by an additional incubation in medium A for 15 min and then in medium B for 10 min with magnetic stirring. The final incubation included medium A for 30 min and then in 100 ml medium B for 20 min with magnetic stirring. We collected the 100-ml medium B and filtered it through a 15-μm nylon mesh. This cell suspension was divided into two 50-ml tube and centrifuged at $175 \times g$ (centrifuge 5800, Kubota, Japan). The supernatant was removed and cell elements was resuspended in medium C and adjusted to 1.5×10^7 cells ml^{-1}. The viability of the cells was assessed by light microscopy using Trypan Blue exclusion, and was confirmed at above 95%.

This cell suspension was used for the elutriation centrifugation. Using a peristatic pump (Masterflex model 7521–40, Cole-Palmer, Chicago, IL), we loaded 5 ml of the cell suspension (7.5×10^7 cells) into the standard separation chamber of a J6-MC centrifuge (Beckman, Tokyo, Japan) equipped with a JE-5.0 rotor system. The initial flow rate was 20 ml min^{-1} and rotor velocity was 2500 rpm at that time. A cell size gradient was formed in the chamber. Four different 50 ml cell fractions were collected at the following flow rates: 20 ml min^{-1} (F0); 26 ml min^{-1} (Fl); 37 ml min^{-1} (F2); 60 ml min^{-1} (rotation stopped) (F3). We repeated this procedure and collected the F2 fraction. Next, the F2 fraction was centrifuged at $175 \times g$, resuspended in medium C, and adjusted to 2×10^6 cells ml^{-1}. Subsequently, the suspension was subjected to a second elutriation step using a Sanderson separation chamber. Ten million cells in 5 ml were injected at a flow rate of 17 ml min^{-1} and rotor velocity was set at 2000 rpm. Four different 50-ml fractions were collected at the following flow rates: 17 ml min^{-1} (SF0); 21 ml min^{-1} (SFl), 28 ml min^{-1} (SF2), and 60 ml min^{-1} (rotation stopped) (SF3). The SF2 fraction was centrifuged at $175 \times g$ and resuspended in 3-ml culture medium to wash the cells. After two washes in the culture medium, the cells were resuspended in culture medium and adjusted to 2×10^5 cells ml^{-1}. The cells were cultured in 24-well plates pre-coated with Matrigel (diluted 1:10 with culture medium) at 10^5 cells per well. The cells were incubated in 500 μl culture medium under a humid atmosphere containing 5% CO_2 and 95% air at 37 °C for 48 h. This incubation time elicited an appropriate gastrin response.

2.4. Secretion studies

After the 48-h cultivation, the culture medium was aspirated and replaced with fresh serum-free and gastrin-free medium. After equilibration for 2 h, the medium was again aspirated and replaced with secretion medium plus test substance and incubated for 1 h. After incubation, the plates were centrifuged at $220 \times g$ for 1 min. The supernatants were collected and stored at −20 °C until measurement of histamine.

2.5. Determination of histamine

Histamine was measured by high-performance liquid chromatography (HPLC)-fluorometry technique (Yamatodani et al., 1985). We collected 50 μl of each culture

supernatant and diluted the samples with 250 μl of 3% perchloric acid and 30 μl of 2 M KOH/1 M KH_2PO_4 in 600 μl tubes. The tubes were stirred and incubated at 4 °C for about 15 min. The samples were then centrifuged at 10,000 rpm for 2 min and 200 μl of each supernatant was collected. A 50-μl aliquot of this supernatant was injected directly into a column packed with TSKgel SP2SW Cation Exchanger (150 × 6 mm i.d.) (Tosoh, Tokyo, Japan). Histamine was eluted with 0.25 M potassium phosphate, at a flow rate of 0.6 ml min^{-1}. The histamine was post-labeled with *o*-phthalaldehyde under alkaline conditions and detected fluorometrically in a F1080 Fluorometer (Hitachi, Tokyo, Japan) using excitation and emission wavelengths of 360 and 450 nm, respectively. The supernatant histamine concentration was determined by comparison to a histamine standard (100 pmol ml^{-1}).

2.6. Determination of intracellular histamine contents

Intracellular histamine contents were measured after complete evaporation of the supernatant. A 500-μl aliquot of 3% perchloric acid was added to each well and scraped by pipette tip. The scraped material was collected in 600-μl tubes to which we added 50 μl of 2 M KOH/1 M KH_2PO_4. The supernatant was collected and measured by the method described above.

2.7. Fluorescent staining of histidine decarboxylase

A drop from each SF2 fraction was applied onto precoated glass slides and dried under a stream of nitrogen. The cell smear was fixed in 4% formalin for 10 min at room temperature, rinsed with Tris bufferd saline (TBS) containing 0.01% Tween20, and then incubated with anti-histidine decarboxylase antibody (1:300 dilution) in phosphate-buffered saline (PBS) containing 0.5% BSA and 0.1% NaN_3 for 1 h at room temperature in a dark room. After rinsing in TBS containing Tween20, fluorescein isothiocyanate (FITC)-conjugated anti-rabbit immunoglobulin G (1:40 dilution) was added for 1 h at room temperature. After rinsing anew, the immunostaining was examined under a fluorescence microscope (Carl Zeiss, Axioskop2 plus). Nonspecific binding was blocked by preincubation with 10% goat serum.

2.8. Determination of intracellular Ca^{2+}

Intracellular Ca^{2+} was measured using highly fluorescent indicators (Grynkiewicz et al., 1985). We assayed intracellular Ca^{2+} levels in Fura-2/acetoxymethylester (AM) (Molecular Probes, Eugene, OR)-loaded ECL cells. In this assay, 0.5×10^6 cells were loaded with 5 μM Fura-2/AM in Ca^{2+}-free Krebs-Ringer-HEPES medium for 20 min at 37 °C. After washing, the cells were stimulated with 10^{-8} M gastrin or 10^{-5} M rabeprazole at 37 °C. Fluorescence was quantified by a Perkin-Elmer LS55 luminescence spectrometer. Excitation was performed at both 340 and 380 nm and emission was determined at 520 nm. Ca^{2+} concentrations were calculated from the ratios of these values. The peak intracellular Ca^{2+} concentration that was transiently achieved was utilized to determine the agonist concentration dependence of the biological responses.

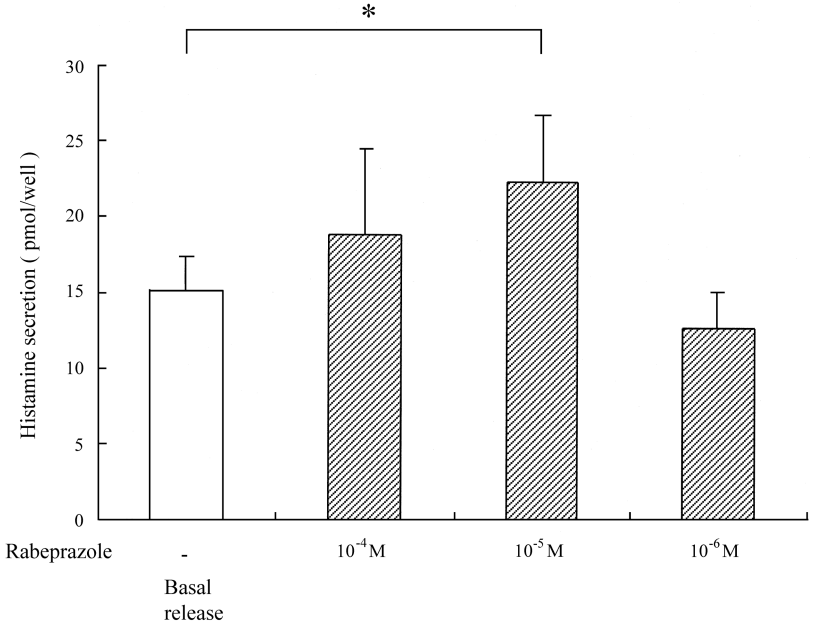

Fig. 1. Histamine concentration in the supernatant of cultured ECL cells was determined by HPLC. Histamine levels induced by 10^{-5} M rabeprazole were significantly higher than basal histamine concentrations. Values represent means ± S.D. ($n = 10$). *$P < 0.01$ compared to the basal histamine release.

2.9. Statistical analysis

The results are expressed as mean ± 1 S.D. Statistical significance was calculated using the post-hoc Dunnett's test. Values of $P < 0.05$ were considered to be significant.

3. Results

3.1. Histamine release

Stimulation time was set at 1 h based on the results of previous studies (Prinz et al., 1993; Lindström et al., 1997). Histamine released when stimulated only by secretion medium was regarded as basal release. At 10^{-5} M, rabeprazole induced a significant increase in histamine release from ECL cells compared to the basal levels (Fig. 1). Histamine levels were monitored upon stimulation by gastrin or rabeprazole every 10 for 60 min. The time course revealed that gastrin increased histamine release immediately, whereas rabeprazole had a more gradual effect, which peaked at a lower level 30 min after stimulation (Fig. 2).

3.2. Intracellular Ca^{2+}

ECL cells that were incubated in culture medium for 48 h were used to monitor intracellular Ca^{2+}. Intracellular Ca^{2+} levels were determined by the ratio of excitation at 340 and 380 nm on a luminescence spectrometer. Gastrin increased intracellular Ca^{2+} concentrations in ECL cells, whereas rabeprazole did not (Fig. 3).

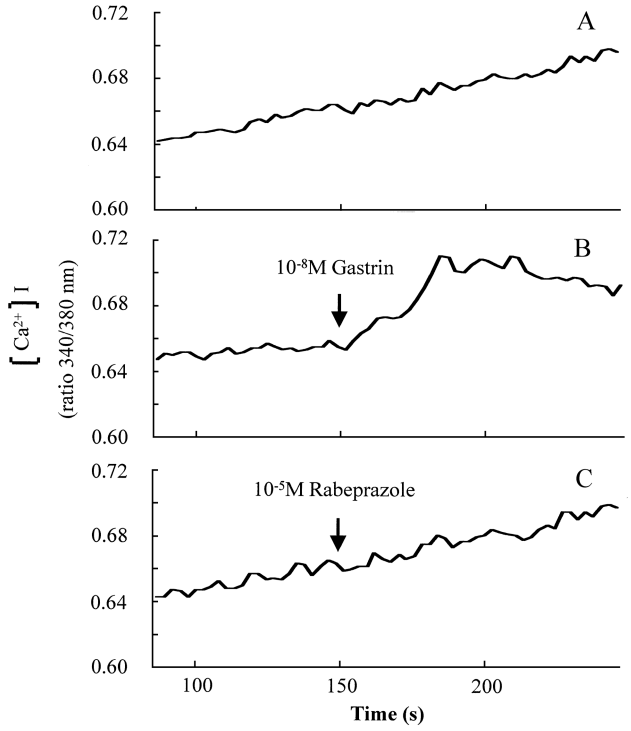

Fig. 3. Changes in intracellular calcium levels. (A) Control, (B) stimulation by gastrin, (C) stimulation by rabeprazole. The ratio of OD value at 340/380 nm increased in response to gastrin, but not rabeprazole, compared with control.

3.3. Histidine decarboxylase activity

Histidine decarboxylase immunofluorescence staining was also monitored in cultured ECL cells to determine the

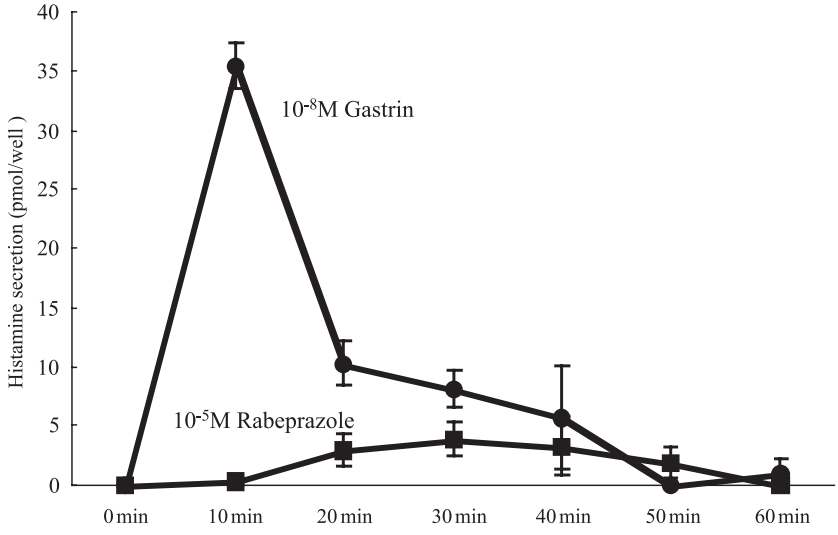

Fig. 2. Timeline of histamine levels induced by gastrin or rabeprazole. Histamine concentrations were monitored every 10 min for 1 h. Data are shown after deducting the basal histamine release. Histamine levels peaked immediately in response to gastrin, whereas the rabeprazole peak was smaller and occurred 30 min after stimulation. Values represent means ± S.D. ($n = 5$).

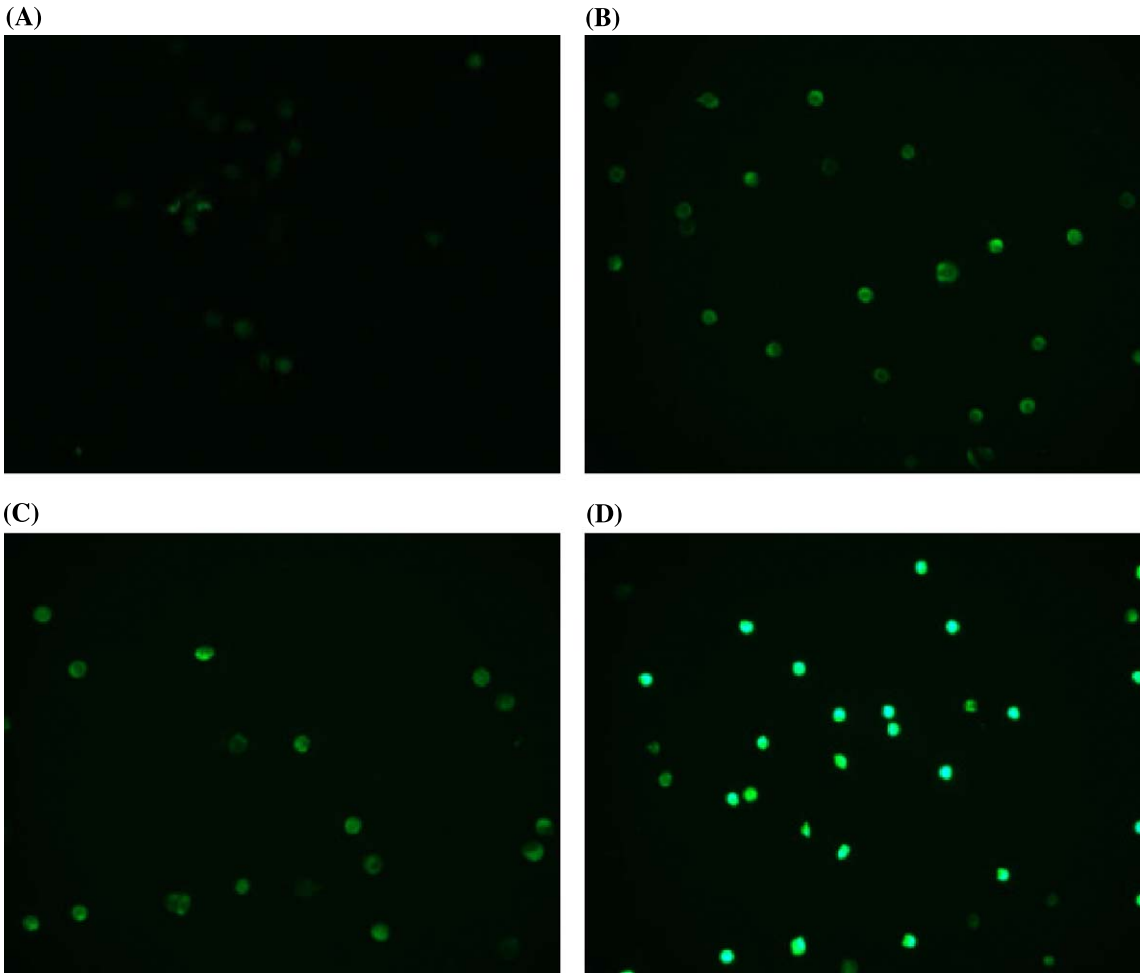

Fig. 4. Histidine decarboxylase immunofluorescence staining. (A) Negative control, (B) basal release, (C) stimulation by rabeprazole, (D) stimulation by gastrin. Exposure to gastrin increased fluorescence intensity over basal levels, whereas stimulation by rabeprazole had no effect.

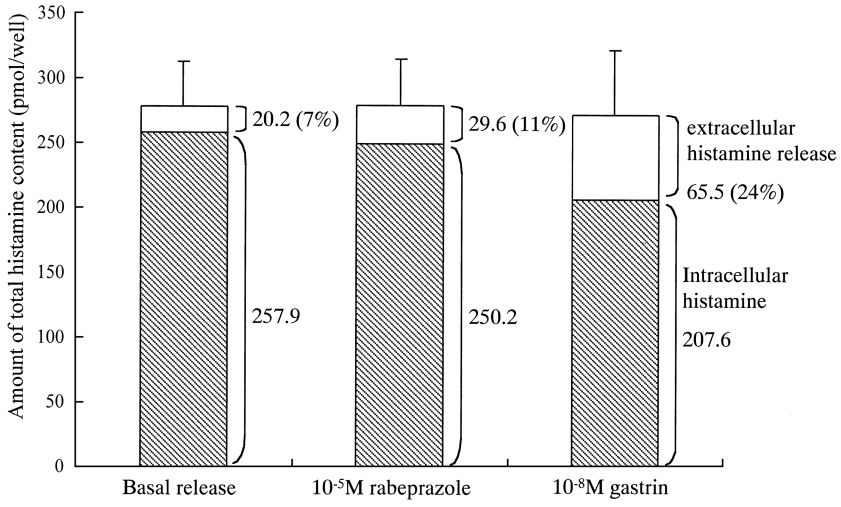

Fig. 5. Total histamine levels. Basal histamine levels released from ECL cells corresponded to about 7% of total intracellular histamine. In contrast, the amount released in response to gastrin and rabeprazole corresponded to about 24% and 11%, respectively. However, total intracellular histamine levels remained stable. Values represent means ± S.D. ($n = 5$).

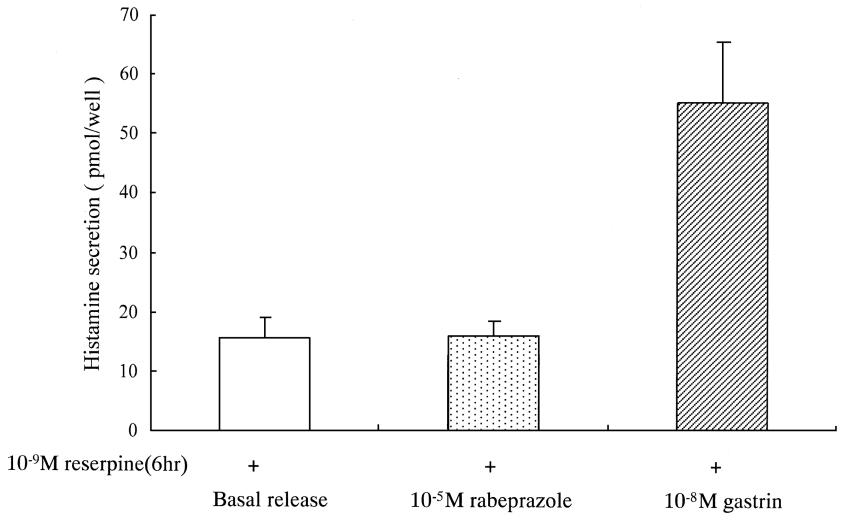

Fig. 6. Effects of reserpine on histamine release. A 6-h preincubation with 10^{-9} M reserpine affected histamine induction by rabeprazole but did not affect basal or gastrin-induced levels. Values represent means ± S.D. ($n = 5$).

effects of rabeprazole on histidine decarboxylase activity. ECL cells were stimulated for 6 h by gastrin or rabeprazole because a previous study demonstrated that histidine decarboxylase activity increased slowly and reached a plateau at 6 h upon stimulation with gastrin in vivo (Håkanson et al., 1994a). Gastrin increased the intensity of histidine decarboxylase immunofluorescence staining compared to basal levels, whereas rabeprazole did not. Goat serum was used as a negative control (Fig. 4).

3.4. Total amount of histamine

The histamine released from ECL cells under basal conditions corresponded to approximately 7% of the total intracellular histamine content. After stimulation by gastrin and rabeprazole, ECL cells released approximately 24% and 11% of the total, respectively. However, no significant difference was observed in the total amount of intracellular histamine under basal conditions or in response to stimulation by gastrin and rabeprazole (Fig. 5).

3.5. Histamine release in response to reserpine

A 6-h preincubation with 10^{-9} M reserpine, an inhibitor of vesicular monoamine transporter 2 (VMAT2), suppressed histamine release in response to rabeprazole but had no effect on basal release or histamine release in response to gastrin (Fig. 6). A decrease in incubation time or reserpine concentration did not affect histamine release, although increased reserpine levels also decreased basal release.

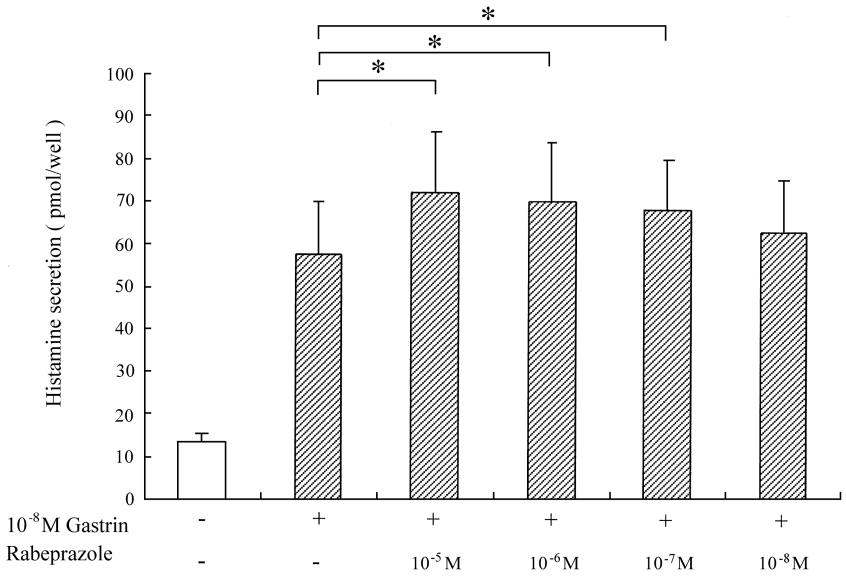

Fig. 7. Histamine release from ECL cells stimulated by both gastrin and rabeprazole. Values represent means ± S.D. ($n = 10$). *$P < 0.05$ compared to the basal histamine release.

3.6. Stimulation by rabeprazole under clinical conditions

In clinical situation, when patients are administered rabeprazole as single oral doses of 20 mg once daily, the maximum serum concentration of the drug is about 10^{-6} M (Yasuda et al., 1994). In the present study, we monitored the effects of lower rabeprazole concentrations administered over a longer period. Gastrin (10^{-8} M) increased histamine release from ECL cells four-fold over basal levels after 48-h culture. These results were in agreement with previously reported data (Lindström and Håkanson, 2001; Lindström et al., 1997). However, the addition of rabeprazole to the 48-h incubation significantly increased the gastrin-induced histamine peak relative to controls (without rabeprazole) (Fig. 7). This may result from an increase in histamine levels in vesicles. However, rabeprazole did not increase histamine levels in ECL cells during the long-term exposure.

4. Discussion

An increase in the histamine content of the oxyntic mucosa in response to proton pump inhibitors was initially attributed to the indirect effects of gastrin on ECL cells (Nakamura et al., 2000; Tari et al., 2002; Kimura et al., 1997). No evidence had been previously presented for direct action of proton pump inhibitors due to numerous interactions that occur in vivo. Recently, a new method for collecting highly purified ECL cells using an elutriator system (Beckman) was developed (Prinz et al., 1993), which enabled investigation of the direct effects of various substances on ECL cells by eliminating interactions in vitro. Previously, histamine release from ECL cells was assumed to be regulated by inhibition of V-type ATPase in secretory vesicles in response to proton pump inhibitors. However, the present study demonstrated that rabeprazole stimulated histamine release directly from ECL cells. The histamine release in response to rabeprazole was much more gradual than that in response to gastrin. The histamine peak in response to gastrin occurred within 10 min, whereas stimulation by rabeprazole induced a maximum 30–40 min later.

Gastrin is known to stimulate intracellular Ca^{2+} concentrations in ECL cells (Prinz et al., 1993; Zanner et al., 2002). The increase in intracellular Ca^{2+} promotes exocytosis and histamine release from secretory vesicles in ECL cells immediately (Prinz et al., 1994). However, histamine release, which is caused by rabeprazole, may be stimulated by a different pathway that does not involve an increase in intracellular Ca^{2+} Indeed, the present study showed that rabeprazole did not increase intracellular Ca^{2+} levels in ECL cells but did induce histamine release. Histidine decarboxylase immunofluorescence was performed to investigate the participation of rabeprazole in histamine synthesis. Histamine is produced by the decarboxylation of histidine by histidine decarboxylase in the cytoplasm of ECL cells, and activation of histidine decarboxylase accelerates histamine synthesis. The histidine decarboxylase staining showed that fluorescence increased over basal levels in response to gastrin but not rabeprazole. This demonstrated that rabeprazole was not involved in histamine synthesis.

Lindström et al. (1997) reported that 25–30% of intracellular histamine is released from ECL cells upon stimulation by gastrin. The present study confirmed that basal histamine release accounted for about 7% of intracellular histamine, and about 24% was released upon stimulation by gastrin. On the other hand, stimulation by rabeprazole induced the release of approximately 11% of total histamine. We observed no change in total histamine content from basal levels upon stimulation by gastrin and rabeprazole. The increase in histamine release in response to rabeprazole was not a result of increased exocytosis or histamine synthesis but was caused by an increase in histamine levels in secretory vesicles. We evaluated this conjecture by examining the response of V-type ATPase to rabeprazole. However, histamine release was not affected by the administration of rabeprazole with bafilomycin, an inhibitor of V-type ATPase (data not shown). This suggested that rabeprazole affects VMAT2 levels in the vesicles. VMAT2 is a 12 transmembrane domain type protein, which is present on the membrane of secretory vesicles. It has the ability to transfer histamine from the cytoplasm into secretory vesicles in exchange for protons (Weithe and Eiden, 2000). Rabeprazole could theoretically promote the transport of histamine into the vesicles by an interaction with VMAT2. Therefore, we investigated changes in histamine release in response to stimulation by rabeprazole and reserpine, a competitive inhibitor of amine transport in vivo and in vitro (Rudnick et al., 1990; Varoqui and Erickson, 1997). A 6-h preincubation with 10^{-9} M reserpine suppressed histamine release in response to rabeprazole but did not affect basal release or stimulation by gastrin. Accordingly, it was considered that the effects of rabeprazole participate in VMAT2.

As mentioned above, the present study demonstrated that rabeprazole directly affected histamine release from ECL cells, although this response was not due to increased intracellular Ca^{2+} levels or histidine decarboxylase activity but resulted possibly from effects on VMAT2. We found that omeprazole, another proton pump inhibitors, had similar effects, although roxatidine (histamine H_2 receptor antagonist) has no direct effect on ECL cells (data not shown).

The increase in histamine did not significantly influence gastric acid secretion because proton pump inhibitors block the final step in this process. However, histamine has several additional functions in the stomach. For example, histamine directly affects vascular dilation and general trophic responses of the oxyntic mucosa (Waldum and Sandvik, 1989). In particular, histamine has various effects on tumors such as glioma (Van der Ven et al., 1993),

bronchogenic carcinoma (Sheehan et al., 1996), renal cell carcinoma (Kokron et al., 1991), and melanoma (Reynolds et al., 1996). Histamine is believed to participate in carcinogenesis by affecting immunological functions including lymphocyte adhesion, cytotoxicity, and cytokine production (Bolton et al., 2000). Histamine may have similar functions in digestive organs. Colon cancer is reportedly stimulated by histamine (Adams et al., 1994), and histamine may play a role in the proliferation of gastric tumors (Watson et al., 1993). Histamine may not have systemic effects due to its low levels, but it may have considerable effects in the stomach because of considerable numbers of ECL cells in this organ. Patients suffering from gastroesophageal reflux disease (Van Rensburg et al., 1998; Laursen et al., 1995) and severe acid peptic disease (Freston, 1997) receive long-term treatment with proton pump inhibitors. However, the present study suggests that histamine release from ECL cells increases in response to long-term proton pump inhibitors treatment, which necessitates further investigation of the potential development of gastric tumors.

References

Adams, W.J., Lawson, J.A., Morris, D.L., 1994. Cimetidine inhibits in vivo growth of human colon cancer and reverses histamine stimulated in vitro and in vivo growth. Gut 35, 1632–1636.

Bolton, E., King, J., Morris, D.L., 2000. H2-antagonists in the treatment of colon and breast cancer. Semin. Cancer Biol. 10, 3–10.

Chen, D., Zhao, C.M., Lindström, E., Håkanson, R., 1999. Rat stomach ECL cells: update of biology and physiology. Gen. Pharmacol. 32, 413–422.

Freston, J.W., 1997. Long-term acid control and proton pump inhibitors: interactions and safety issues in perspective. Am. J. Gastroenterol. 92, 51S–55S.

Grynkiewicz, G., Poenie, M., Tsien, R.Y., 1985. A new generation of Ca^{2+} indicators with greatly improved fluorescence properties. J. Biol. Chem. 260, 3440–3450.

Håkanson, R., Chen, D., Andersson, K., Monstein, H.J., Zhao, C.M., Ryberg, B., Sundler, F., Mattsson, H., 1994a. The biology and physiology of the ECL cell. Yale J. Biol. Med. 67, 123–134.

Håkanson, R., Chen, D., Tielemans, Y., Andersson, K., Ryberg, B., Sundler, F., Mattsson, H., 1994b. ECL cells: biology and pathobiology. Digestion 55 (Suppl. 3), 38–45.

Hersey, S.J., Sachs, G., 1995. Gastric acid secretion. Physiol. Rev. 75, 155–189.

Kimura, K., Chen, D., Lindström, E., Yamada, H., Zhao, C.M., Håkanson, R., 1997. Functional impairment of the individual rat stomach ECL cell in response to sustained hypergastrinemia. Regul. Pept. 72, 69–77.

Kokron, O., Maca, S., Gasser, G., Schmidt, P.R., 1991. Cimetidine and coumarin therapy of renal cell carcinoma. A pilot study. Oncology 48, 102–106.

Laursen, L.S., Havelund, T., Bondesen, S., Hansen, J., Sanchez, G., Sebelin, E., Fenger, C., Lauritsen, K., 1995. Omeprazole in the long-term treatment of gastro-esophageal reflux disease. Scand. J. Gastroenterol. 30, 839–846.

Lindström, E., Håkanson, R., 2001. Neurohormonal regulation of secretion from isolated rat stomach ECL cells: a critical reappraisal. Regul. Pept. 97, 169–180.

Lindström, E., Björkqvist, M., Boketoft, Å., Chen, D., Zhao, C.M., Kimura, K., Håkanson, R., 1997. Neurohormonal regulation of histamine and pancreastatin secretion from isolated rat stomach ECL cells. Regul. Pept. 71, 73–86.

Lindström, E., Chen, D., Norlén, P., Andersson, K., Håkanson, R., 2001. Control of gastric acid secretion: the gastrin-ECL cell-parietal cell axis. Comp. Biochem. Physiol., Part A Mol. Integr. Physiol. 128, 505–514.

Misunashi, K., Furukawa, Y., Katano, K., Abe, K., 1993. Effect of omeprazole, an inhibitor of H^+, K^+-ATPase, on bone resorption in humans. Calcif. Tissue Int. 53, 21–25.

Nakamura, S., Watanabe, H., Yokota, T., Matsui, H., Onji, M., Maeyama, K., 2000. Effect of rabeprazole on histamine synthesis in enterochromaffin-like cells of mast cell-deficient (Ws/Ws) rats. Eur. J. Pharmacol. 394, 9–16.

Prinz, C., Kajimura, M., Scott, D.R., Mercier, F., Helander, H.F., Sachs, G., 1993. Histamine secretion from rat enterochromaffin-like cells. Gastroenterology 103, 449–461.

Prinz, C., Scott, D.R., Hurwitz, D., Helander, H.F., Sachs, G., 1994. Gastrin effects on isolated rat enterochromaffin-like cells in primary culture. Am. J. Physiol. 267, G663–G675.

Prinz, C., Zanner, R., Gerhard, M., Mahr, S., Neumayer, N., Hohne-Zell, B., Gratzl, M., 1999. The mechanism of histamine secretion from gastric enterochromaffin-like cells. Am. J. Physiol. 277, C845–C855.

Reynolds, J.L., Akhter, J., Morris, D.L., 1996. In vitro effect of histamine and histamine H1 and H2 receptor antagonists on cellular proliferation of human malignant melanoma cell lines. Melanoma Res. 6, 95–99.

Rudnick, G., Steiner-Mordoch, S.S., Fishkes, H., Stern-Back, Y., Schuldiner, S., 1990. Energetics of reserpine binding and occlusion by the chromaffin granule biogenic amine transporter. Biochemistry 29, 603–608.

Sheehan, P.F., Baker, T., Tutton, P.J., Barkla, D.H., 1996. Effects of histamine and 5-hydroxytryptamine on the growth rate of xenografted human bronchogenic carcinomas. Clin. Exp. Pharmacol. Physiol. 23, 465–471.

Tari, A., Kawano, M., Kodama, K., Yonei, Y., Okahara, S., Haruma, K., Sumii, K., Kajiyama, G., 2002. The effects of rabeprazole on parietal cells and enterochromaffin-like cells in rats: a comparison with omeprazole. J. Gastroenterol. 37, 177–185.

Van der Ven, L.T., Prinsen, I.M., Jansen, G.H., Roholl, P.J., Defferrari, R., Slater, R., Den Otter, W., 1993. Growth of cultured human glioma tumour cells can be regulated with histamine and histamine antagonists. Br. J. Cancer 68, 475–483.

Van Rensburg, C.J., Honiball, P.J., Van Zyl, J.H., Grundling, H.D., Eloff, F.P., Spies, S.K., Simjee, A.E., Theron, I., Fischer, R., Louw, J.A., 1998. Safety and efficacy of pantoprazole 40 mg daily as relapse prophylaxis in patients with healed reflux oesophagitis—a 2-year follow-up. Aliment. Pharmacol. Ther. 13, 1023–1028.

Varoqui, H., Erickson, J.D., 1997. Vesicular neurotransmitter transporters. Mol. Neurobiol. 15, 165–191.

Waldum, H.L., Sandvik, A.K., 1989. Histamine and the stomach. Scand. J. Gastroenterol. 24, 130–139.

Watson, S.A., Wilkinson, L.J., Robertson, J.F., Hardcastle, J.D., 1993. Effect of histamine on the growth of human gastrointestinal tumours: reversal by cimetidine. Gut 34, 1091–1096.

Weithe, E., Eiden, L.E., 2000. Chemical neuroanatomy of the vesicular amine transporters. FASEB J. 14, 2435–2449.

Yamatodani, A., Fukuda, H., Wada, H., 1985. High-performance liquid chromatographic determination of plasma and brain histamine without previous purification of biological samples: cation-exchange chromatography coupled with post-column derivatization fluorometry. J. Chromatogr. 344, 115–123.

Yasuda, S., Ohnishi, A., Ogawa, T., Tomono, Y., Hasegawa, J., Nakai, H., Shimamura, Y., Morishita, N., 1994. Pharmacokinetic properties of E3810, a new proton pump inhibitor, in healthy male volunteers. Int. J. Clin. Pharmacol. Ther. 32, 466–473.

Zanner, R., Hapfelmeier, G., Grantzl, M., Prinz, C., 2002. Intracellular signal transduction during gastrin-induced histamine secretion in rat gastric ECL cells. Am. J. Physiol. Cell Physiol. 282, C374–C382.