ELSEVIER

European Journal of Pharmacology 392 (2000) 23–29

ejp

www.elsevier.nl/locate/ejphar

Histamine H_3 receptor-mediated inhibition of endogenous acetylcholine release from the isolated, vascularly perfused rat stomach

Kunihiko Yokotani *, Yoshinori Murakami, Shoshiro Okada, Muchun Wang, Kumiko Nakamura

Department of Pharmacology, Kochi Medical School, Nankoku, Kochi 783-8505, Japan

Received 23 September 1999; received in revised form 20 January 2000; accepted 25 January 2000

Abstract

We studied the effects of histamine H_3 receptor ligands on the release of endogenous acetylcholine from the isolated, vascularly perfused rat stomach. The stomach was perfused via the celiac artery with modified Krebs–Ringer solution containing physostigmine. Released acetylcholine from the portal vein was electrochemically measured using high-performance liquid chromatography and an enzyme system. Vagus nerves were electrically stimulated twice for 2 min (0.5 or 2.5 Hz). Acetylcholine release evoked at 2.5 Hz was slightly inhibited by histamine and effectively potentiated by thioperamide, a histamine H_3 receptor antagonist. Acetylcholine release evoked at 0.5 Hz in the presence of atropine was not influenced by thioperamide, but effectively inhibited by histamine, *R*-α-methylhistamine or imetit, histamine H_3 receptor agonists. These inhibitory effects were abolished by thioperamide or pertussis toxin. These results suggest that histamine attenuates acetylcholine release from vagus nerves through histamine H_3 receptor-mediated and pertussis toxin-sensitive mechanisms in the rat stomach.

Keywords: Acetylcholine release; Stomach; Histamine H_3 receptor; Pertussis toxin

1. Introduction

Histamine is an important physiological regulator in central and peripheral tissues (Schwartz et al., 1991; Rangachari, 1992). Its various effects are mediated by different receptor subtypes of which three (H_1, H_2 and H_3) have been identified (Hill et al., 1997). The third subtype of histamine receptor (H_3) was originally described in the brain, where it negatively controls both histamine synthesis and release (Arrang et al., 1983). Subsequently, following the development of selective agonists and antagonists (Arrang et al., 1987; Garbarg et al., 1992; Howson et al., 1992; Van der Goot et al., 1992; Vollinga et al., 1994), the histamine H_3 receptor was also discovered in peripheral tissues such as perivascular nerves (Ishikawa and Sperelakis, 1987), ileum (Trzeciakowski, 1987; Menkveld and Timmerman, 1990) and lung (Ichinose et al., 1989).

The discovery of histamine H_3 receptors promoted investigators to re-examine the activity of histamine at a gastric level. In vivo studies carried out in conscious cats indicated that the histamine H_3 receptor agonist *R*-α-methylhistamine inhibits acid secretion stimulated by pentagastrin or peptone meal (Bado et al., 1991) and also by 2-deoxy-D-glucose (Coruzzi et al., 1991). This effect of *R*-α-methylhistamine was prevented by thioperamide, a histamine H_3 receptor antagonist, suggesting the involvement of histamine H_3 receptors in gastric acid secretion. In an attempt to gain a deeper insight into the role of histamine H_3 receptors in the cellular mechanisms regulating acid secretion, many investigators carried out further studies using in vitro preparations; however, data obtained for different preparations and species are controversial: *R*-α-methylhistamine and thioperamide were ineffective in the rat isolated stomach (Coruzzi et al., 1992), whereas in isolated rabbit gastric gland, the presence of inhibitory histamine H_3 receptors was demonstrated on histamine-containing cells and parietal cells (Bado et al., 1992, 1995). In isolated mouse stomach, histamine inhibits somatostatin release via histamine H_3 receptors and augments acid secretion by eliminating the inhibitory influence of somatostatin (Vuyyuru and Schubert 1997).

* Corresponding author. Tel.: +81-88-880-2328; fax: +81-88-880-2328.

0014-2999/00/$ - see front matter
PII: S0014-2999(00)00085-6

In the present experiments, we examined the effects of histamine H_3 receptor ligands on acetylcholine release from vagus nerves using the isolated, vascularly perfused rat stomach.

2. Materials and methods

2.1. Perfusion experiments

Male Wistar rats weighing about 350 g were housed for at least 2 weeks in a conditioned room and fasted overnight before the experiments were performed. Details of the experimental procedures were as described elsewhere (Yokotani et al., 1993). Briefly, under urethane anesthesia, the abdomen was opened with a midline incision. After ligation of the abdominal aorta just above where the celiac artery branches, a cannula was inserted into the celiac artery via an incision placed on the opposite side of the aorta and modified Krebs–Ringer solution bubbled with a mixture of 95% O_2 and 5% CO_2 maintained at pH 7.4 and 37°C was perfused at a constant flow rate of 2.5 ml/min. Modified Krebs–Ringer solution was composed of 117.5 mM NaCl, 4.7 mM KCl, 2.4 mM $CaCl_2$, 1.1 mM $MgCl_2$, 1.1 mM NaH_2PO_4, 25 mM $NaHCO_3$, 11.1 mM glucose and 100 μM physostigmine, a cholinesterase inhibitor. Bilateral vagus nerves around the esophagus were carefully dissected and cut 1 cm above the cardia. The esophagus, duodenum, spleen and pancreas were dissected after ligation of the vessels, and the vascularly perfused stomach was kept in a chamber prewarmed at 37°C. After an equilibration period of 60 min, each 2-min effluent from the portal vein was collected in chilled tubes containing 200 pmol of isopropylhomocholine as an internal standard and 250 μl of 1 M phosphoric acid to maintain the samples at pH 3–4.

In each experiment, bilateral vagus nerves were electrically stimulated twice with square-wave pulses at 0.5 or 2.5 Hz, supramaximal intensity (10 mA), 2 ms duration, for 2 min using platinum ring electrodes. The first stimulation was applied 4 min after the start of sampling and the second stimulation was carried out 26 min after the first stimulation. Perfusion medium containing test substances was changed 14 min before the second stimulation.

In some experiments, rats were pretreated with pertussis toxin (10 μg per rat dissolved in 0.1 ml of sodium phosphate-buffered saline, pH 7.0, 4 days before experiments) or vehicle injected into the dorsal penic vein under light ether anesthesia, as described in our previous paper (Yokotani and Osumi, 1993).

2.2. Tissue analysis

At the end of each experiment, the stomach was homogenized in 20 ml of cold 0.1 N perchloric acid containing 16.8 mg of disodium EDTA and 50 nmol of isopropylhomocholine as an internal standard, using a Polytron homogenizer. The homogenate was centrifuged for 10 min with $14{,}000 \times g$ at 4°C. An aliquot of the supernatant was analyzed to determine the tissue level of acetylcholine (see Section 2.3).

2.3. Acetylcholine determination

Acetylcholine released into the perfusate and that remaining in the stomach at the end of experiments were measured with a combination of high-performance liquid chromatography (HPLC), enzyme reaction and electrochemical detection (Potter et al., 1983). A solution that consisted of 0.1 M Na_2HPO_4, pH 8.5, containing 300 mg/l sodium l-decanesulfonate and 65 mg/l tetramethylammonium chloride was delivered as the mobile phase at a rate of 1.0 ml per min. After separation on a styrene polymer column (AC-GEL, Eicom, Kyoto, Japan), acetylcholine was converted to hydrogen peroxide by a post-column enzyme reactor (AC-Enzympak, Eicom) with immobilized acetylcholinesterase and choline oxidase. The separation column and enzyme reactor were controlled isothermally at 33°C. The hydrogen peroxide was detected with an electrochemical detector (ECD-100, Eicom) equipped with a platinum electrode. The electrode potential was set at +450 mV against an Ag/AgCl reference electrode. The amount of acetylcholine was calculated by using a peak height ratio relative to that of isopropylhomocholine. The least detectable amount was 0.5 pmol.

2.4. Evaluation and statistical analysis

The release of acetylcholine from the stomach is expressed as pmol/2 min stomach^{-1} or percentage of its tissue content in the stomach. Basal release was calculated by averaging the amount released in two subsequent samples before stimulation. The amount of evoked release of acetylcholine above the basal level during 12 min after the first or second stimulation is expressed as S_1 or S_2. The effects of test substances applied during the second stimulation are expressed as the ratio of S_2 to S_1. All values are expressed as means ± SEM.

All data were analyzed by repeated-measure analysis of variance, followed by post-hoc analysis with Bonferroni method for comparing a control with all other means. *P*-values of less than 0.05 were taken to indicate significance.

2.5. Drugs

The substances used in this study included atropine sulfate, histamine dihydrochloride, physostigmine hemisulfate (Sigma, St. Louis, MO, USA); imetit dihydrobromide, pertussis toxin, *R*(−)-α- methylhistamine dihydrochloride, thioperamide maleate (Research Biochemicals, Natick, MA, USA); isopropy1homocholine iodide (Eicom); sodium

1-decanesulfonate (Nakalai Tesque, Kyoto, Japan); tetramethylammonium chloride (Aldrich, Milwaukee, WI, USA).

All other reagents and solvents were of HPLC grade or the highest grade available (Nakalai Tesque).

3. Results

3.1. Effects of histamine or thioperamide, a blocker of histamine H_3 receptors, on the release of acetylcholine evoked by vagal stimulation at 2.5 Hz

Basal release of acetylcholine was 7.45 ± 0.75 pmol/2 min stomach^{-1} (0.05 ± 0.01% of tissue content) ($n = 29$) (Fig. 1). Electrical stimulation of the vagus nerves at 2.5 Hz evoked an increase of acetylcholine release (about 150 pmol/2 min stomach^{-1}) that rapidly declined to the basal level as described in our previous paper (Yokotani et al., 1993). Repetitive stimulation evoked consistent and reproducible increases in acetylcholine release (Fig. 1A).

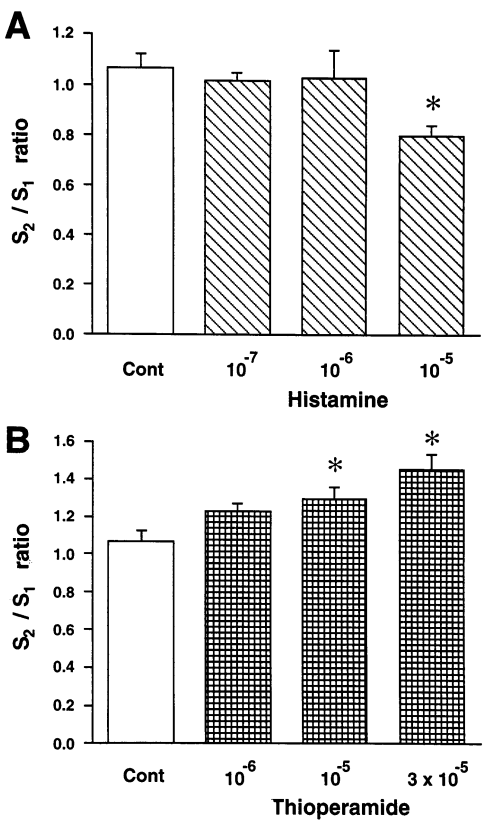

Fig. 1. Effects of histamine or thioperamide on the evoked release of acetylcholine from the isolated stomach. The vagus nerves were stimulated twice at 2.5 Hz for 2 min: the first stimulation was carried out in normal medium; the second stimulation was carried out in the presence of histamine (A) or thioperamide (B). The first and second stimulation-evoked release of acetylcholine above the basal level is expressed as S_1 and S_2. Effects of these agents are expressed as the ratio of S_2 to S_1. (A) Control (Cont) ($n = 6$): Histamine; 10^{-7} M ($n = 4$), 10^{-6} M ($n = 4$), 10^{-5} M ($n = 4$). (B) Control (cited from A): Thioperamide; 10^{-6} M ($n = 4$), 10^{-5} M ($n = 4$), 3×10^{-5} M ($n = 3$). Values are the means $\pm$SEM.* A significant difference from the control ($P < 0.05$).

After the first stimulation of the vagus nerve, the medium was changed to the next one containing histamine (10^{-7}–10^{-5} M) or thioperamide (10^{-6}–3×10^{-5} M). Basal release of acetylcholine was not significantly affected by these agents. Histamine (10^{-7}–10^{-6} M) had no effect, but a higher concentration (10^{-5} M) of histamine slightly but significantly reduced the evoked release of acetylcholine (Fig. 1A).

Thioperamide (10^{-6}–3×10^{-5} M) concentration-dependently potentiated the evoked release of acetylcholine (Fig. 1B).

3.2. Effects of histamine or thioperamide on the release of acetylcholine evoked by vagal stimulation at 0.5 Hz in the presence of atropine

Basal release of acetylcholine in the presence of 10^{-6} M atropine was 10.42 ± 1.46 pmol/2 min stomach^{-1} (0.05 ± 0.01% of tissue content) ($n = 20$) (Fig. 2). The amount of acetylcholine released in response to vagal stimulation at 0.5 Hz in the presence of atropine was almost the same as that evoked by vagal stimulation at 2.5 Hz. Repetitive stimulation of the vagus nerves at 0.5 Hz evoked reproducible increases in the release of acetylcholine.

After the first stimulation, the medium was changed to the next one containing histamine (10^{-7}–10^{-5} M) or thioperamide (3×10^{-5} M). Basal release of acetylcholine was not affected by these agents. Histamine (10^{-7}–10^{-5} M) effectively inhibited the evoked release of acetyl-

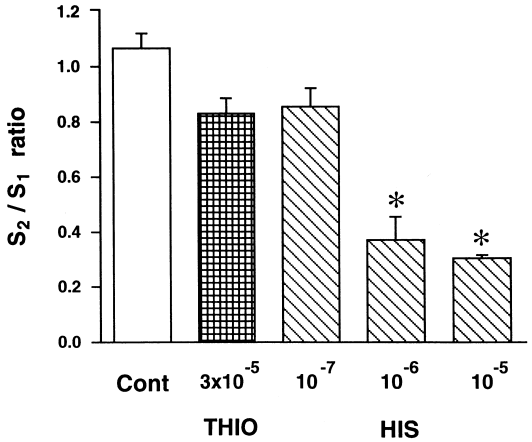

Fig. 2. Effects of histamine (HIS) or thioperamide (THIO) on the evoked release of acetylcholine from the isolated stomach. The vagus nerves were stimulated twice at 0.5 Hz for 2 min in the presence of 10^{-6} M atropine: the first stimulation was carried out in normal medium; the second stimulation was carried out in the presence of histamine or thioperamide. Control (Cont) ($n = 4$), Histamine; 10^{-7} M ($n = 4$), 10^{-6} M ($n = 4$), 10^{-5} M ($n = 4$). Thioperamide; 3×10^{-5} M ($n = 4$). Other conditions were the same as those for Fig. 1.

choline in a concentration-dependent manner (Fig. 2). Thioperamide (3×10^{-5} M) had no effect on the evoked acetylcholine release.

3.3. Effects of R-α-methylhistamine or imetit, agonists of histamine H_3 receptors, on the release of acetylcholine evoked by vagal stimulation at 0.5 Hz in the presence of atropine

After the first stimulation of the vagus nerve at 0.5 Hz in the presence of 10^{-6} M atropine, the medium was changed to the next one containing *R*-α-methylhistamine (10^{-7}–3×10^{-5} M) or imetit (10^{-8}–10^{-5} M). Basal release of acetylcholine was not affected by these agents.

R-α-methylhistamine effectively inhibited the evoked release of acetylcholine in a concentration-dependent manner (Fig. 3A). Imetit also effectively and concentration-dependently inhibited the evoked release of acetylcholine (Fig. 3B). The inhibitory potency of imetit was greater than that of α-methylhistamine.

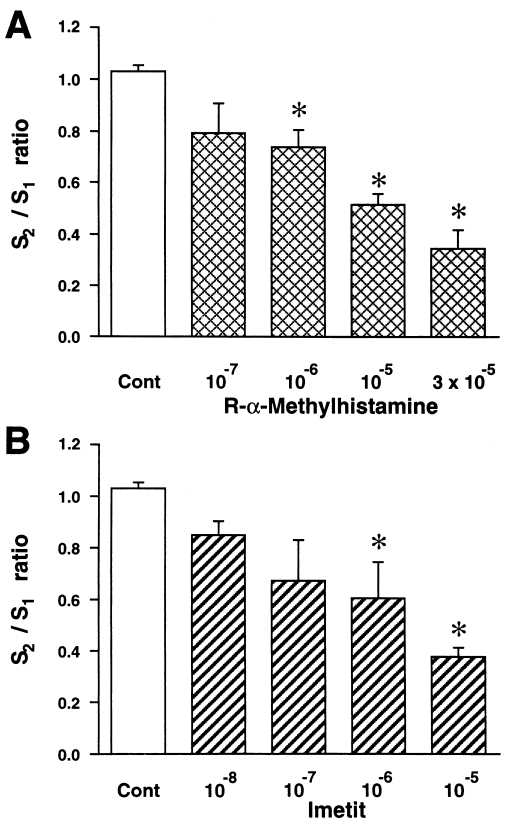

Fig. 3. Effects of *R*-α-methylhistamine or imetit on the evoked release of acetylcholine. The vagus nerves were stimulated twice at 0.5 Hz for 2 min in the presence of 10^{-6} M atropine: the first stimulation was carried out in normal medium; the second stimulation was carried out in the presence of *R*-α-methylhistamine (A) or imetit (B). (A) Control (Cont) ($n = 4$) (cited from Fig. 2): *R*-α-methylhistamine; 10^{-7} M ($n = 4$), 10^{-6} M ($n = 4$), 10^{-5} M ($n = 4$), 3×10^{-5} M ($n = 5$). (B) Control (Cont) ($n = 4$) (cited from Fig. 2): Imetit; 10^{-8} M ($n = 4$), 10^{-7} M ($n = 4$), 10^{-6} M ($n = 5$), 10^{-5} M ($n = 4$). Other conditions were the same as those for Figs. 1 and 2.

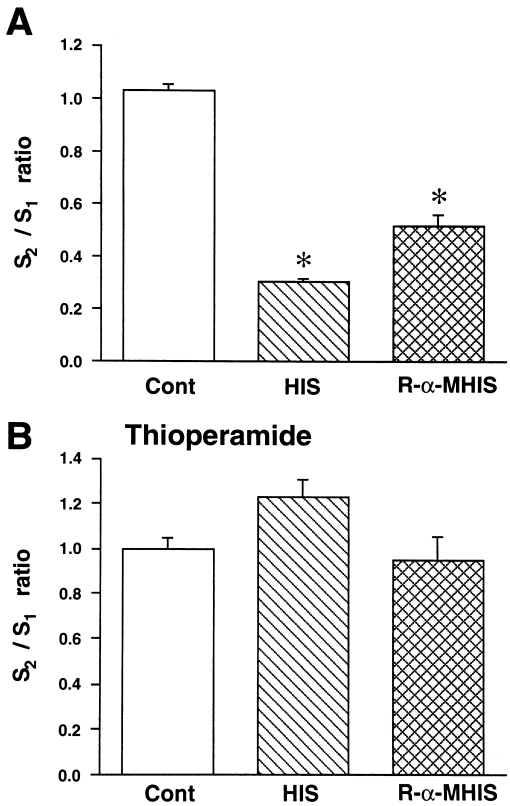

Fig. 4. Effects of thioperamide on histamine (HIS)- or *R*-α-methylhistamine (α-MHIS)-induced inhibition of acetylcholine release. The vagus nerves were stimulated twice at 0.5 Hz for 2 min in the presence of 10^{-6} M atropine. (A) The effect of histamine (10^{-5} M) or *R*-α-methylhistamine (10^{-5} M) on the release of acetylcholine in normal medium. Control (Cont) ($n = 4$) (cited from Fig. 2): 10^{-5} M Histamine ($n = 4$) (cited from Fig. 2): 10^{-5} M *R*-α-methylhistamine ($n = 6$) (cited from Fig. 3A). (B) The effect of histamine (10^{-5} M) or *R*-α- methylhistamine (10^{-5} M) on the release of acetylcholine in the presence of thioperamide (3×10^{-5} M). Thioperamide was administered throughout the experiment. Control (Cont) ($n = 5$), 10^{-5} M Histamine ($n = 6$), 10^{-5} M *R*-α-methylhistamine ($n = 5$). Other conditions were the same as those for Figs. 1–3.

3.4. Effects of thioperamide, a histamine H_3 receptor antagonist, on histamine- or R-α-methylhistamine-induced inhibition of the release of acetylcholine evoked by vagal stimulation at 0.5 Hz in the presence of atropine

Thioperamide (3×10^{-5} M) was administered throughout the experiments (Fig. 4B). After the first stimulation, the medium was changed to the next one containing histamine (10^{-5} M) or *R*-α-methylhistamine (10^{-5} M). Thioperamide (10^{-6} M) abolished the inhibitory effect of histamine or *R*-α-methylhistamine on the evoked release of acetylcholine (Fig. 4B).

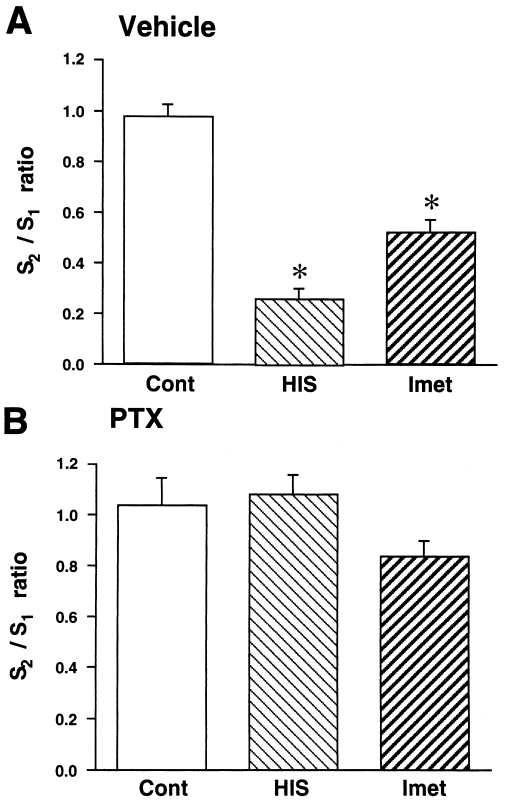

Fig. 5. Effects of pertussis toxin on histamine (HIS)- or imetit (Imet)-induced inhibition of acetylcholine release. The vagus nerves were stimulated twice at 0.5 Hz for 2 min in the presence of 10^{-6} M atropine. (A) The effect of histamine (10^{-5} M) or imetit (10^{-5} M) on acetylcholine release from vehicle-treated stomach. Control (Cont) ($n=4$), 10^{-5} M Histamine ($n=5$), 10^{-5} M Imetit ($n=4$). (B) The effect of histamine (10^{-5} M) or imetit (10^{-5} M) on acetylcholine release from pertussis toxin (PTX)-treated stomach. Pertussis toxin (10 μg/rat) was intravenously applied 4 days before experiments. Control (Cont) ($n=4$), 10^{-5} M Histamine ($n=5$), 10^{-5} M Imetit ($n=4$). Other conditions were the same as those for Figs. 1–4.

3.5. Effects of pertussis toxin on histamine- or imetit-induced inhibition of the release of acetylcholine evoked by vagal stimulation at 0.5 Hz in the presence of atropine

In the preparations treated with vehicle alone, histamine (10^{-5} M) or imetit (10^{-5} M) also effectively inhibited the evoked release of acetylcholine (Fig. 5A).

In the preparations treated with pertussis toxin, the inhibitory effects of 10^{-5} M histamine or 10^{-5} M imetit on the evoked release of acetylcholine disappeared.

4. Discussion

After the discovery of histamine H_2 receptors, it became clear that histamine plays a fundamental role in the control of gastric acid secretion. Immunological studies have revealed histamine-storing cells in gastric tissue, i.e., mast cells in mammals including humans, enterochromaffin-like cells in rodents (Håkanson et al., 1983; Panula et al., 1985; Prinz et al., 1993). The location of these cells, in the vicinity of the parietal cells, is consistent with a paracrine route for triggering parietal histamine H_2 receptors. Vagal nerve stimulation has been shown to increase venous histamine release from the isolated, vascularly perfused rat stomach by activation of muscarinic M_2 receptors (Sandvik et al., 1988). Gastrin release is also stimulated by the cholinergic nervous system (Schubert et al., 1992; Yokotani et al., 1995) and released gastrin could play a role in histamine release from these histamine-containing cells (Bergqvist and Öbrink, 1979; Sandvik et al., 1989).

Since the histamine H_3 receptor agonist *R*-α-methylhistamine had no effect on gastric secretion in pylorus-ligated rats or on the secretion stimulated by histamine, pentagastrin and 2-deoxy-D-glucose in the lumen-perfused rat stomach, it has been suggested that the histamine H_3 receptor is not involved in the regulation of acid secretion in rats (Coruzzi et al., 1992). In the present study, histamine also had a weak inhibitory effect on the release of acetylcholine evoked by vagal stimulation at 2.5 Hz, but thioperamide, an antagonist of histamine H_3 receptors (Arrang et al., 1987; Hew et al., 1990), effectively potentiated the evoked release of acetylcholine. From these results, a possibility arose that the vagally mediated release of endogenous histamine had already influenced the release of acetylcholine by activation of histamine H_3 receptors.

To examine this hypothesis, we examined the effect of exogenous histamine in the presence of atropine to avoid the effect of endogenous histamine. Since inhibitory muscarinic M_3 autoreceptors are present on the vagus nerve terminals (Yokotani et al., 1993), the vagus nerves were stimulated at 0.5 Hz in the presence of atropine. The amount of acetylcholine released in response to vagal stimulation at 0.5 Hz in the presence of atropine was almost the same as that evoked by vagal stimulation at 2.5 Hz. The release of acetylcholine evoked under these conditions was not influenced by thioperamide, but effectively attenuated by histamine. The histamine H_3 receptor agonists, *R*-α-methylhistamine (Arrang et al., 1987) and imetit (Garbarg et al., 1992; Howson et al., 1992; Van der Goot et al., 1992), also effectively inhibited the evoked release of acetylcholine. It has been reported that thioperamide and imetit show relatively high affinity for the 5-hydroxytryptamine 5-HT_3 receptor and sigma receptor in addition to the histamine H_3 receptor (Jansen et al., 1994; Leurs et al., 1995) and that thioperamide increases GABA release from the rat hypothalamus by affecting neural GABA uptake (Yamamoto et al., 1997). In contrast, histamine and *R*-α-methylhistamine are selective for histamine H_3 receptor (Jansen et al., 1994). In the present experiment, the histamine- or *R*-α-methylhistamine-induced inhibition was abolished by thioperamide. From these results, it seems likely that activation of histamine H_3 receptors, probably located on the vagus nerves, attenuates the release of

acetylcholine from vagus nerve terminals in the rat stomach. Histamine H_3 receptor-mediated inhibition of acetylcholine release was also demonstrated in guinea pig myenteric plexus (Poli et al., 1991).

The histamine H_3-receptor, which was recently cloned from the human thalamus library (Lovenberg et al., 1999), belongs to the superfamily of G-protein-coupling receptors. The direct evidence for a functional H_3–receptor–G–protein linkage has come from studies of [^{35}S]GTPγS binding to rat cerebral cortical membranes (Clark and Hill, 1996). In the presence of H_1- and H_2-receptor-antagonists, both *R*-α-methylhistamine and N^{α}-methylhistamine produced a concentration-dependent stimulation of [^{35}S]-GTPγS binding in a pertussis toxin-sensitive manner, implying direct coupling to a G_i or G_o protein. In the human gastric cell line HGT1, *R*-α-methylhistamine inhibited basal and carbachol-stimulated inositol phosphate formation in a pertussis toxin-sensitive manner (Cherifi et al., 1992). In the present experiments, the histamine- or imetit-induced inhibition of acetylcholine release was abolished by pertussis toxin. Therefore, it is likely that histamine inhibits acetylcholine release by histamine H_3 receptor-G-protein-coupling mechanisms.

In conclusion, the observation reported here provides evidence for the presence of a histamine H_3 receptor subtype on the vagus nerves in the rat stomach. Activation of this receptor inhibits the release of acetylcholine by a pertussis toxin-sensitive mechanism.

References

Arrang, J.M., Garbarg, M., Lancelot, J.C., Lecomte, J.M., Pollard, H., Robba, M., 1987. Highly potent and selective ligands for histamine H_3-receptors. Nature 327, 117–123.

Arrang, J.M., Garbarg, M., Schwartz, J.C., 1983. Autoinhibition of brain histamine release mediated by a novel class (H_3) of histamine receptor. Nature 302, 832–837.

Bado, A., Hervatin, F., Lewin, M.J., 1991. Pharmacological evidence for histamine H_3 receptor in the control of gastric acid secretion in cats. Am. J. Physiol. 260, G631–G635.

Bado, A., Laigneau, J.P., Moizo, L., Cherifi, Y., Lewin, M.J., 1995. H_3-receptor activation inhibits cholinergic stimulation of acid secretion in isolated rabbit fundic glands. J. Pharmacol. Exp. Ther. 275, 1099–1103.

Bado, A., Moizo, L., Laigneau, J.P., Lewin, M.J., 1992. Pharmacological characterization of histamine H_3 receptors in isolated rabbit gastric glands. Am. J. Physiol. 262, G56–G61.

Bergqvist, E., Öbrink, K.J., 1979. Gastrin-histamine as a normal sequence in gastric acid stimulation in the rabbit. Upsala J. Med. Sci. 84, 145–154.

Cherifi, Y., Pigeon, C., Le Romancer, M., Bado, A., Reyl-Desmars, F., Lewin, M.J., 1992. Purification of a histamine H_3-receptor negatively coupled to phosphoinositide turnover in the human gastric cell line HGT1. J. Biol. Chem. 267, 25315–25320.

Clark, E.A., Hill, S.J., 1996. Sensitivity of histamine H_3-receptor agonist-stimulated [^{35}S]GTPγS binding to pertussis toxin. Eur. J. Pharmacol. 296, 223–225.

Coruzzi, G., Adami, M., Bertaccini, G., 1992. Histamine H_3-receptors are not involved in the regulation of rat gastric secretion. Pharmacology 44, 190–195.

Coruzzi, G., Bertaccini, G., Schwartz, J.C., 1991. Evidence that histamine H_3-receptors are involved in the control of gastric acid secretion in the conscious cat. Naunyn-Schmiedeberg's Arch. Pharmacol. 343, 225–227.

Garbarg, M., Arrang, J.M., Rouleau, A., Ligneau, X., Tuong, M.D., Schwartz, J.C., Ganellin, C.R., 1992. *S*[2-(4-imidazolyl)ethyl]isothiourea, a highly specific and potent histamine H_3-receptor agonist. J. Pharmacol. Exp. Ther. 263, 304–310.

Håkanson, R., Wahlestedt, C., Westlin, L., Vallgren, S., Sundler, F., 1983. Neuronal histamine in the gut wall releasable by gastrin and cholecystokinin. Neurosci. Lett. 42, 305–310.

Hew, R.W., Hodgkinson, C.R., Hill, S.J., 1990. Characterization of histamine H_3-receptors in guinea-pig ileum with H_3-selective ligands. Br. J. Pharmacol. 101, 621–624.

Hill, S.J., Ganellin, C.R., Timmerman, H., Schwartz, J.C., Shankley, N.P., Young, L.M., Schunack, W., Levi, R., Haas, H.L., 1997. International union of pharmacology: XIII. Classification of histamine receptors. Pharmacol. Rev. 49, 253–278.

Howson, W., Parsons, M.E., Ravel, P., Swayne, G.T.G., 1992. Two novel and potent and selective histamine H_3-receptor agonists. Bioorg. Med. Chem. Lett. 2, 77–79.

Ichinose, M., Stretton, C.D., Schwartz, J.C., Barnes, P.J., 1989. Histamine H_3-receptors inhibit cholinergic neurotransmission in guinea-pig airways. Br. J. Pharmacol. 97, 13–15.

Ishikawa, S., Sperelakis, N., 1987. A novel class (H_3) of histamine receptors on perivascular nerve terminals. Nature 327, 158–160.

Jansen, F.P., Wu, T.S., Voss, H.P., Steinbusch, H.W., Vollinga, R.C., Rademaker, B., Bast, A., Timmerman, H., 1994. Characterization of the binding of the first selective radiolabelled histamine H_3-receptor antagonist, [^{125}I]-iodophenpropit, to rat brain. Br. J. Pharmacol. 113, 355–362.

Leurs, R., Tulp, M.T., Menge, W.M., Adolfs, M.J., Zuiderveld, O.P., Timmerman, H., 1995. Evaluation of the receptor selectivity of the H_3 receptor antagonists, iodophenpropit and thioperamide: an interaction with the 5-HT_3 receptor revealed. Br. J. Pharmacol. 116, 2315–2321.

Lovenberg, T.W., Roland, B.L., Wilson, S.J., Jiang, X., Pyati, J., Huvar, A., Jackson, M.R., Erlander, M.G., 1999. Cloning and functional expression of the human histamine H_3-receptor. Mol. Pharmacol. 55, 1101–1107.

Menkveld, G.J., Timmerman, H., 1990. Inhibition of electrically evoked contractions of guinea-pig ileum preparations mediated by the histamine H_3-receptor. Eur. J. Pharmacol. 186, 343–347.

Panula, P., Kaartinen, M., Macklin, M., Costa, E., 1985. Histamine-containing peripheral neuronal and endocrine systems. J. Histochem. Cytochem. 33, 933–941.

Poli, E., Coruzzi, G., Bertaccini, G., 1991. Histamine H_3-receptors regulate acetylcholine release from the guinea pig ileum myenteric plexus. Life Sci. 48, PL63–PL68.

Potter, P.E., Meek, J.L., Neff, N.H., 1983. Acetylcholine and choline in neuronal tissue measured by HPLC with electrochemical detection. J. Neurochem. 41, 188–194.

Prinz, C., Kajimura, M., Scott, D.R., Mercier, F., Helander, H.F., Sachs, G., 1993. Histamine secretion from rat enterochromaffin-like cells. Gastroenterology 105, 449–461.

Rangachari, P.K., 1992. Histamine: mercurial messenger in the gut. Am. J. Physiol. 262, G1–G13.

Sandvik, A.K., Kleveland, P.M., Waldum, H.L., 1988. Muscarinic M_2 stimulation releases histamine in the totally isolated, vascularly perfused rat stomach. Scand. J. Gastroenterol. 23, 1049–1056.

Sandvik, A.K., Lewin, M.J., Waldum, H.L., 1989. Histamine release in the isolated vascularly perfused stomach of the rat: regulation by autoreceptors. Br. J. Pharmacol. 96, 557–562.

Schwartz, J.C., Arrang, J.M., Garbarg, M., Pollard, H., Ruat, M., 1991. Histaminergic transmission in the mammalian brain. Physiol. Rev. 71, 1–51.

Schubert, M.L., Coy, D.H., Makhlouf, G.M., 1992. Peptone stimulates

gastrin secretion from the stomach by activating bombesin/GRP and cholinergic neurons. Am. J. Physiol. 262, G685–G689.

Trzeciakowski, J.P., 1987. Inhibition of guinea pig ileum contractions mediated by a class of histamine receptor resembling the H_3 subtype. J. Pharmacol. Exp. Ther. 243, 874–880.

Van der Goot, H., Schepers, M.J.P., Sterk, G.J., Timmerman, H., 1992. Isothiourea analogues of histamine as potent agonists or antagonists of histamine H_3-receptor. Eur. J. Med. Chem. 27, 511–517.

Vollinga, R.C., de Koning, J.P., Jansen, F.P., Leurs, R., Menge, W.M., Timmerman, H., 1994. A new potent and selective histamine H_3-receptor agonist, 4-(1*H*-imidazol-4-ylmethyl)piperidine. J. Med. Chem. 37, 332–333.

Vuyyuru, L., Schubert, M.L., 1997. Histamine, acting via H_3 receptors, inhibits somatostatin and stimulates acid secretion in isolated mouse stomach. Gastroenterology 113, 1545–1552.

Yamamoto, Y., Mochizuki, T., Okakura-Mochizuki, K., Uno, A., Yamatodani, A., 1997. Thioperamide, a histamine H_3-receptor antagonist, increases GABA release from the rat hypothalamus. Methods Find. Exp. Clin. Pharmacol. 19, 289–298.

Yokotani, K., DelValle, J., Park, J., Yamada, T., 1995. Muscarinic M_3 receptor-mediated release of gastrin from canine antral G cells in primary culture. Digestion 56, 31–34.

Yokotani, K., Okuma, Y., Nakamura, K., Osumi, Y., 1993. Release of endogenous acetylcholine from a vascularly perfused rat stomach in vitro: inhibition by M_3 muscarinic autoreceptors and alpha-2 adrenoceptors. J. Pharmacol. Exp. Ther. 266, 1190–1195.

Yokotani, K., Osumi, Y., 1993. Cholinergic M_2 muscarinic receptor-mediated inhibition of endogenous noradrenaline release from the isolated vascularly perfused rat stomach. J. Pharmacol. Exp. Ther. 264, 54–60.