The Gastric H₃ Receptor: A Review

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Received May 11, 1992

Previous in vivo and in vitro studies from our laboratory have revealed a line of pharmacological evidence supporting histamine H₃ receptor(s) involvement in the control of gastric acid secretion. We have recently extended our studies to the human gastric tumoral cell HGT-1. This cell was found to contain an H₃ receptor inhibiting basal and carbachol-stimulated inositol phosphate formation. Furthermore, we were able to solubilize and affinity-purify this receptor in the form of a single 70 kDa protein. These findings are the first biochemical description of the H₃ receptor subtype and the first direct demonstration that this subtype can occur on the non-neural cell. Furthermore, they provide a molecular basis to explain its suggested inhibitory role in gastric physiology.

INTRODUCTION

The novel "H₃" histamine receptor subtype was originally characterized on brain histaminergic nerves as an autoreceptor downregulating histamine synthesis and release [1]. The localization of this receptor was, however, rapidly extended to serotonergic, cholinergic, and non-cholinergic fibers, in brain as well as in peripheral tissues such as airways, lung, and intestine [2,3].

We summarize here recent studies from our laboratory, supporting the hypothesis that H₃ receptors are very likely to be involved in the control of gastric acid secretion. Furthermore, we report preliminary results on biochemical and functional characterization of a gastric H₃ receptor in the human gastric cell line HGT-1.

PHARMACOLOGICAL EVIDENCE

The first evidence for a gastric H₃ receptor subtype came from in vivo studies carried out in our laboratory on fistula cats by Hervatin et al. [4] and Bado et al. [5]. These studies showed that stimulation of acid secretion by meal or pentagastrin was potently and dose-dependently inhibited by the specific H₃ agonist Rα-methylhistamine (Ra-MeHA). Furthermore, this inhibition was itself inhibited by the specific H₃ antagonist thioperamide (Figs. 1, 2). The fact that Ra-MeHA inhibited pentagastrin stimulation suggests that the putative H₃ receptor(s) should be located downstream of the gastrin receptor. Furthermore, an extrinsic cholinergic vagal mediation is apparently excluded, since similar findings were observed for the main stomach and the denervated Heidenhain pouch.

The possibility that Ra-MeHA inhibition of (penta)gastrin stimulation could be mediated by histamine cell H₃ receptors was investigated by Sandvik et al. on the isolated rat stomach [6]. These authors found that Ra-MeHA inhibited basal and

Abbreviation: Ra-MeHA: Rα-methylhistamine

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gastrin-stimulated vascular histamine release in a ranitidine-insensitive manner (Fig. 2). This finding is consistent with the presence of an H₃ autoreceptor on the histamine-secreting cell, in agreement with the report of H₃ autoreceptors on brain histaminergic nerves [1] and with the early suggestion by Håkanson et al. that histamine inhibits its own synthesis and release in the gastric mucosa [7]. The intervention of an H₂-type receptor was previously postulated because the stimulation of gastric mucosal histamine release, evoked by pentagastrin injection in the rat, was reported to be increased after infusion of metiamide, burimamide, or cimetidine [8,9]. These findings, which contrast with the lack of effect of ranitidine in the in vitro

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**FIG. 1.** Dose-dependent inhibition for the H₃-receptor agonist (Rα)-methylhistamine (Rα-MeHA) on pentagastrin-stimulated gastric acid secretion from the main stomach in cats with gastric fistula. Redrawn from [5].

**FIG. 2.** Effect of H₃-receptor agonist (Rα)-methylhistamine (Rα-MeHA) alone or together with the H₃-receptor antagonist, thioperamide (Thioperamide) on bactopeptone (BP) meal-stimulated gastric acid secretion from the denervated Heidenhain pouch in conscious cats. Redrawn from [5].
study of Sandvik et al. [6], might be, however, inherent in the in vivo situation and the doses used.

Evidence for H₃ modulation of other mediators of acid secretion was investigated on the same experimental model by Moizo et al. [10]. These studies demonstrated that Rα-MeHA strongly potentiated carbachol-induced vascular gastrin release and that this effect was totally suppressed by thioperamide. Such a finding might be interpreted as evidence for an H₃ receptor on the gastrin cell. Since in this study, Rα-MeHA concomitantly reversed carbachol inhibition of somatostatin release, however, gastrin release potentiation could be secondary to this effect. Thus, in addition to its putative location on the histamine-secreting cell, the H₃ receptor could also occur on other gastric endocrine cells, such as gastrin and somatostatin cells.

In an attempt to gain a deeper insight into the role of H₃ receptors in the cellular mechanisms regulating acid secretion, we carried out further studies on isolated rabbit gastric glands [11]. We found that Rα-MeHA inhibited and thioperamide enhanced basal histamine release (Fig. 3), in agreement with the suggested existence of an inhibitory H₃ receptor on gastric histamine cells. In addition, thioperamide-enhanced histamine release was accompanied by the stimulation of ¹⁴C-aminopyrine accumulation by the glands. Thioperamide stimulation of ¹⁴C-aminopyrine accumulation was still present, however, after blockade of the parietal cell H₂ receptor by ranitidine (Fig. 3). Moreover, Rα-MeHA also inhibited carbachol- and even histamine-stimulated ¹⁴C-aminopyrine accumulation (Fig. 4). These findings do not conflict with the presence of an H₃ receptor on histaminocytes but argue strongly for the additional presence of an H₃ receptor on the parietal cell itself (Fig. 4).

**BIOCHEMICAL EVIDENCE**

A direct demonstration of gastric H₃ receptor(s) was recently attempted in our laboratory, using the human gastric tumoral cell HGT-1. The great suitability of this model for the study of gastric acid secretion receptors, particularly histamine H₂ and somatostatin receptors had been previously shown [12,13,14]. Using ³H[Nα-MeHA as
a receptor ligand, Cherifi et al. [15] characterized high-affinity specific binding sites of an equilibrium constant ($K_D$) of $0.85 \pm 0.06$ nM and $2 \pm 0.5$ nM in the absence and the presence of GTP($\gamma$)S, respectively. They were able to solubilize these sites and to purify them further (86 percent purity), using a thioperamide affinity column. The binding of $^3$(H)$\alpha$-MeHA to the purified sites showed a $K_D$ of $1.6 \pm 0.1$ nM. It was competitively displaced by $\alpha$-MeHA ($IC_{50} = 5.8$ nM), $R\alpha$-MeHA ($IC_{50} = 9 \pm$ nM), and thioperamide ($IC_{50} = 85 \pm 10$ nM) but not by GTP($\gamma$)S, nor the $H_2$ and $H_1$ antagonists famotidine and mepyramine, respectively. On the other hand, Cherifi et al. demonstrated a thioperamide-sensitive, ranitidine-insensitive inhibition of basal and carbachol-stimulated inositol phosphate formation by $R\alpha$-MeHA in the HGT-1 cell (Fig. 5) [15].

These findings are the first direct evidence for the existence of $H_3$ receptors as a distinct biochemical entity and for the occurrence of this receptor on a non-neural cell. They further support the hypothesis that this novel receptor subtype is negatively coupled to phosphatidylinositol turnover, a signaling pathway consistent with its general inhibitory action, as reported in the above studies.
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