Lack of histamine alters gastric mucosal morphology: comparison of histidine decarboxylase-deficient and mast cell-deficient mice

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Lack of histamine alters gastric mucosal morphology: comparison of histidine decarboxylase-deficient and mast cell-deficient mice. *Am J Physiol Gastrointest Liver Physiol* 287: G1053–G1061, 2004. First published July 22, 2004; doi:10.1152/ajpgi.00353.2003.—Histamine plays an important role in the regulation of gastric acid secretion; however, its role in maintenance of gastric morphology remains unclear. To clarify the necessity of histamine for gastric mucosal development and maintenance, we evaluated two different kinds of mice that lacked either mast cells (one of the gastric histamine-producing cell types) or histidine decarboxylase (HDC; a histamine-synthesizing enzyme). Measurements of stomach weight, intragastric pH, mucosal histamine levels, as well as serum gastrin and albumin levels were performed in mice. Gastric mucosal appearance was examined by immunohistochemical techniques. Although gastric mucosal histamine levels in mast cell-deficient mice were half of those observed in the wild-type mice, intragastric pH, serum gastrin levels, and gastric morphology at 12 mo were unchanged compared with the wild-type mice. In contrast, HDC-deficient mice possessed no detectable gastric histamine, but did exhibit hypergastrinemia, as well as marked increases in intragastric pH and stomach weight compared with the wild-type mice. Histological analysis revealed that 9-mo-old HDC-deficient mice demonstrated hyperplasia in the oxyntic glandular base region, as well as increased numbers of parietal and enterochromaffin-like cells. These results indicate that enterochromaffin-like cell-derived histamine is potentially involved in gastric mucosal morphology regulation.

enterochromaffin-like cell; parietal cell; hypergastrinemia

GASTRIC MUCOSA CONSISTS OF numerous blind tubular units containing various cell types (28). All gastric mucosal epithelial cells are known to originate from common progenitor cells in the proliferative zone of the isthmus. Some cells migrate upward, becoming mucous-secreting surface epithelial cells, whereas other cells migrate toward the base of the gland, differentiating into parietal, chief, or endocrine cells (18). Maintenance of gastric mucosal integrity and structure is regulated by a variety of endocrine- and paracrine-mediating factors.

Histamine is synthesized from histidine by histidine decarboxylase (HDC) and is stored in mast cells, enterochromaffin-like (ECL) cells, and enteric nerve fibers in the oxyntic mucosa of rodent stomachs (25, 46). It is well established that histamine plays a pivotal role in gastric acid secretion (1, 47); however, its role in the regulation of gastric mucosal proliferation and differentiation essentially remains uncharacterized. To clarify such a role, previous reports (16, 39, 40) have used pharmacological inhibitors of histamine pathways, such as histamine receptor (H1R, H2R, and H3R) antagonists and α-fluoromethylhistidine (α-FMH), an irreversible inhibitor of HDC (4, 5, 10). Nonetheless, incomplete elimination of histamine action by these inhibitors could potentially confuse analysis of the exact role of histamine for regulation of gastric mucosal morphology.

Recently, HDC-deficient (HDC-KO) mice have been generated by gene-targeting methods (45, 52). As expected, these mice exhibited no de novo gastric mucosal histamine synthesis (52). Using 8- to 12-wk-old HDC-KO mice, we reported that gastric mucosal morphology was similar to the wild-type (WT) mice (52), although HDC-KO mice showed hypopacy and hypergastrinemia (24, 52). In this study, we examined the role of histamine in the regulation of gastric mucosal morphology in HDC-KO mice longer term, from 1 to 9 mo. In addition, the present study characterized the specific role of ECL cell-derived histamine by comparing the difference between HDC-KO mice and mast cell-deficient mice.

MATERIALS AND METHODS

Animals. Six-week-old male mast cell-deficient WBB6F1-W/Wv (W/Wv) and congenic normal WBB6F1-+/+ (+/+) mice were purchased (Japan SLC, Shizuoka, Japan). The two mice strains were independently maintained until an age of 3 or 12 mo. Male HDC-KO as well as the WT littermate mice were generated on a mixed genetic 129/Sv times ICR background, and raised with regular diet, and independently maintained until an age of 1, 3, 6, or 9 mo (24, 45, 52). All of the mice were given standard pellets (CE-2; CLEA, Tokyo, Japan). Mice were deprived of food for 21 h and water for 2 h before each experiment. Plasma and tissue samples from pairs of age-matched WT and mutant mice were compared. Animal maintenance and experimental procedures were carried out in accordance with the guidelines of the Ethics Committee of Kyoto Pharmaceutical University.

Measurement of serum gastrin and albumin levels, as well as intragastric pH. Blood collected from mice was centrifuged at 6,000 g for 15 min to obtain serum samples. Serum gastrin levels were determined by a radioimmunoassay (Mitsubishi Kagaku Bio-Clinical Laboratories, Tokyo, Japan) and expressed as picograms of gastrin per
milliliter of serum. Serum albumin levels were determined by a bromcresol green assay (6, 21) and expressed as grams of albumin per deciliter of serum. Stomachs removed from mice were incised along the greater curvature, and intragastric pH was measured by directly placing a pH meter on the fundic mucosa.

**Determination of gastric mucosal histamine levels.** Each sample for histamine quantification was collected according to a previously reported method (29). In brief, each stomach was rinsed with PBS containing 10^{-4} M semicarbazide hydrochloride, weighed, and homogenized in 0.01 M PBS. The homogenates were diluted 1:10 with phosphate buffer and heated in boiling water for 10 min to release bound histamine. The homogenates were then centrifuged at 3,300 g for 20 min, and the resulting supernatants were used for measurements. Quantification of sample histamine levels was performed with a histamine enzyme immunoassay kit (Immunotech, Marseilles, France).

**Measurement of gastric mucosal protein and DNA levels.** To measure gastric mucosal protein levels, the entire glandular stomach of each mouse was homogenized with 1 ml of 10 mM sodium phosphate buffer (pH 7.5) containing 1 mM NaCl, 1% Triton X-100, 0.1% SDS, 0.5% deoxycholate, 0.1% apotinin, 10 μg/ml leupeptin, and 1 mM PMSF. The homogenates were centrifuged at 10,000 g for 30 min at 4°C. The protein levels for each supernatant were measured with a protein quantification kit (BioRad, Hercules, CA) and expressed as milligrams of protein per stomach. To quantify DNA levels, high molecular weight DNA was first isolated by digestion of the stomach with proteinase K, followed by phenol-chloroform extraction. The concentration of DNA solubilized in water was then quantified from the absorbance at 260 nm and the DNA levels in gastric mucosa was calculated and expressed as micrograms of DNA per stomach. The ratios of the protein levels or the DNA levels between HDC-KO and WT mice (KO/WT ratio) were calculated and compared each ratio to evaluate whether it is hyperplasia (increased DNA levels) or hypertrophy (increased cell volume, but not DNA levels).

**Treatment.** To evaluate the role played by hypergastrinemia in gastric oxyntic mucosal hyperplasia induced in HDC-KO mice, (R)-1-[2,3-dihydro-1-(2'-methylphenacyl)-2-oxo-5-phenyl-1H-1,4-benzo diazepin-3-yl]-3-(methylphenyl) (YM022) urea from Yamanouchi Pharmaceutical (Tokyo, Japan) (31, 41) was administered orally for 2 mo to 1-mo-old HDC-KO mice. YM022 represents a selective cholecystokinin type 2 receptor (CCK-R) antagonist; a dose of 30 mg·kg^{-1·}day^{-1} was used, because this dose inhibited gastrin-17-stimulated gastric acid secretion in mice by >80% in our preliminary experiments. Omeprazole was administered orally at a dose of 30 mg·kg^{-1·}day^{-1} for 2 mo to 1-mo-old WT mice to induce hypergastrinemia and allow comparison with HDC-KO mice in terms of hyperplasia. Both drugs were suspended in 0.5% hydroxypropylcellulose solution and were administered once daily at a volume of 5 ml/kg body wt.

**Histochecmical analysis.** For hematoxylin and eosin staining, as well as immunohistochemical analysis of the gastric mucosa, the stomach samples were fixed with Carnoy’s fixative overnight, embedded in paraffin wax, and then sectioned at a slice thickness of 4 μm. Paraffin sections stained with hematoxylin and eosin or periodic acid Schiff were used for determination of gastric mucosal thickness. Under a microscope, well-orientated regions spanning from the gastric base to the oxyntic mucosal surface were selected for measurement. The mucosal thickness was taken as the average of measurements in four different visual fields for each stomach with the use of a calibrated-eyepeice micrometer scale. Immunohistochemical analysis of parietal and endocrine cells was performed for each section with the use of the following avidin-biotin-peroxidase immunohistochemical technique. Parietal, D, and endocrine cells were detected with a murine monoclonal antibody for α-subunit of murine H^+·K^+-ATPase (Medical and Biological Laboratories, Nagoya, Japan), a rabbit antibody for somatostatin (DAKO, Carpenteria, CA), and a rabbit anti-body for a peptide (359–389 amino acid) of rat chromogranin A (Cg A; Yamaihar Institute, Fujinomiya, Japan), respectively. In brief, endogenous peroxidase activity was blocked with a methanol solution containing 0.3% hydrogen peroxide. Sections were incubated with primary antibody for α subunit of H^+·K^+-ATPase or Cg A for 2 h at room temperature. Sections were then incubated with secondary biotinylated antibodies, followed by streptavidin peroxidase. Finally, slides were developed with diaminobenzidine and counterstained with hematoxylin. Parietal and endocrine cell counts were quantified in samples in which mucosal glands were perpendicularly oriented to the mucosal surface. Cell counts for parietal cells positively immunoreactive for H^+·K^+-ATPase were determined in four different gland units for each stomach; results were expressed as the number of cells per gland unit. Cell counts for endocrine cells positively immunoreactive for Cg A or D cells positively reactive for somatostatin were determined in four different visual fields for each stomach; results were expressed as the average number of cells per visual field (0.25 mm^2). An average for each group of animals was also calculated.

**Statistics.** Data are expressed as means ± SE. Statistical differences were evaluated by using the Student’s t-test and Dunnett's multiple comparison test, with a P value < 0.05 regarded as significant. Dunnett's test was performed after a significant ANOVA had been achieved.

**RESULTS**

**Mast cell deficiency exerted no effect on gastric morphology.** Deletion of mast cells (W/W^v) caused a significant decrease in gastric mucosal histamine levels by ~50% compared with +/+ mice (Fig. 1A). However, the reduction in histamine levels did not affect intragastric pH (Fig. 1B) or serum gastrin levels (Fig. 1C), which were found to be similar for both +/+ and W/W^v mice. In addition, histological analysis revealed that W/W^v mice failed to exhibit any morphological alterations in the gastric oxyntic mucosa, even 3 and 12 mo after birth (Fig. 1, D–G). Ulcer was observed only in the gastric antrum of W/W^v mice (data not shown), corresponding with the previous report by Shimada et al. (49).

**Long-term histamine deficiency resulted in gastric mucosal hyperplasia, hypochlorhydria, and hypergastrinemia in HDC-KO mice.** HDC-KO mice developed without any obvious abnormality in general appearance, exhibiting body weight gain similar to WT mice for ≤9 mo after birth. As expected, HDC-KO mice possessed undetectable histamine in the stomach (Fig. 2A). It was of interest that intragastric pH in HDC-KO mice was significantly higher than that measured in WT mice at all time points examined (1, 3, 6, and 9 mo after birth; Fig. 2B). In addition, HDC-KO mice exhibited a marked age-dependent gastric weight gain compared with WT mice, which was first obvious 3 mo after birth (Fig. 2C). Moreover, HDC-KO mice serum gastrin levels remained markedly elevated at all time points examined (Fig. 2D). Serum albumin levels were similar for WT and HDC-KO mice 6 and 9 mo after birth (Fig. 2E). No correlation was observed between body weight and stomach weight in either the WT or HDC-KO mice.

To thoroughly ascertain the increased stomach weight observed in HDC-KO mice, gastric mucosal protein and DNA levels were compared for 6-mo-old WT and HDC-KO mice. Protein levels in HDC-KO mice were significantly higher than those of WT mice (17.47 ± 1.89 mg/stomach vs. 11.80 ± 0.74 mg/stomach; KO/WT, 1.48). DNA levels in HDC-KO mice were approximately two times higher than those of WT mice.
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Fig. 1. Histamine levels (A), intragastric pH (B), and serum gastrin levels (C) in 3-mo-old wild-type (WT; +/-) and mast cell-deficient (W/Wv) mice. Values are means ± SE, n = 5–8. *Significant differences from WT mice with P < 0.05. D–G: histological comparison of gastric oxyntic mucosa in 3 (D and E) and 12-mo-old (F and G) +/- (D and F) and W/Wv (E and G) mice. Paraffin-embedded sections were prepared with hematoxylin and eosin staining (bar = 100 μm).

(982.1 ± 172.7 vs. 490.7 ± 49.9 μg/stomach; KO/WT, 2.00). These data indicate that the increase in HDCKO mice stomach weight resulted from an increased number of gastric mucosal cells (hyperplasia), rather than an expanded cellular volume (hypertrophy).

Increased number of parietal and endocrine cells in HDC-KO mice. To identify the predominant cell types present in the hyperplastic mucosa of HDC-KO mice, histochemical analysis was performed. Six months after the birth of HDC-KO mice, their stomachs demonstrated a statistically significant increase in gastric mucosal thickness compared with WT mice. Interestingly, periodic acid Schiff staining revealed that the change in mucosal thickness was most prominent in the glandular basal region (WT, 389.0 ± 11.2 μm vs. HDC-KO, 570.0 ± 29.4 μm; Fig. 3, A–C, filled column). In contrast, no remarkable differences were observed in the pit region (WT, 74.8 ± 6.2 vs. HDC-KO, 74.5 ± 3.9 μm; Fig. 3, A–C, open column).

Time-course analysis revealed that gastric mucosal thickness in HDC-KO mice significantly increased after 1 mo compared with that of WT mice (Figs. 4A; 5, A and B; and 6, A and B), correlating with the increase in stomach weight (Fig. 2C). The hyperplastic changes were observed in the oxyntic mucosa but not in the antrum (Fig. 6, A and B). In addition, immunohistochemical analysis revealed that, in the oxyntic mucosa of HDC-KO mice, there were marked increases in the density of Cg A-positive endocrine cells (Figs. 4B; 5, C and D; and 6) and H+K+-ATPase α-subunit-positive parietal cells (Figs. 4C and 5, E and F), compared with WT mice in a time-dependent manner. Cg A-positive endocrine cells in WT mice mainly distributed in the glandular basal region of the oxyntic mucosa (Fig. 6A). In contrast, in HDC-KO mice, distribution of the positive cells extended throughout the thickened mucosa (Fig. 6B). Interestingly, the size of parietal cells in HDC-KO mice was clearly smaller than that observed in WT mice, although no change in the size of the nucleus was noted (Fig. 5, G and H). In contrast, the density of somatostatin-positive D cell in gastric oxyntic mucosa was similar for HDC-KO and WT mice (data not shown). These results indicate that mucosal hyperplasia observed in HDC-KO mice resulted from increased numbers of Cg A-positive ECL and parietal cells.

Contribution of hypergastrinemia to gastric mucosal hyperplasia induced in HDC-KO mice. To examine the role played by hypergastrinemia for the hyperplastic changes observed in HDC-KO mice, pharmacological analysis was performed with omeprazole and YM022. Omeprazole treatment at a dose of 30 mg/kg once daily for 2 mo to 1-mo-old WT mice resulted in increases in serum gastrin levels (Fig. 7A), gastric mucosal thickness (Fig. 7B), and the number of Cg A-positive (Fig. 7C) and parietal cells (Fig. 7D), compared with vehicle-treated WT mice. In contrast, serum gastrin levels in vehicle-treated HDC-KO mice increased to similar levels observed in omeprazole-treated WT mice (Fig. 7A). Nonetheless, it was interesting to note that vehicle-treated HDC-KO mice exhibited more significant increases in mucosal thickness (Fig. 7B) and the number of Cg A-positive (Fig. 7C) and parietal cells (Fig. 7D) than omeprazole-treated WT mice. Treatment of HDC-KO mice with YM022 recovered the histological parameters to the levels in omeprazole-treated WT mice, but not to the levels in vehicle-treated WT mice. It should also be noted that YM022 augmented the increase in serum gastrin levels induced in HDC-KO mice.

DISCUSSION

The present study demonstrated that long-term histamine deficiency ≈9 mo attained with HDC deletion led to gastric mucosal morphological alteration with time. As a matter of fact, apparent oxyntic mucosal hyperplasia, i.e., increases in parietal and Cg A-positive endocrine cell counts, was observed in HDC-KO mice. Gastric mucosal thickening mainly resulted from changes that developed in the glandular base region of the gastric mucosa. In addition, gastric mucosal cells in HDC-KO...
mice, especially parietal cells, were observed to be smaller in size than the cells in WT mice. Some of the above observations were consistent with the previous three different gene-targeted mice studies including HDC-KO (27), gastrin-deficient (26), and our H2 receptor-deficient (H2R-KO) mice (29, 44). Hunyady et al. (27) reported an increase in the number of parietal cells in HDC-KO mice at 9 mo old. Both H2R-KO and gastrin-deficient mice are reported to possess defects in ECL cell function, i.e., histamine production (26, 29, 44). H2R-KO mice impair the entry of histamine signal from ECL cells into the parietal cells, and subsequently exhibited an increased stomach weight, enlarged gastric folds with cystic dilatation, hyperplasia of smaller-sized parietal and ECL cells, and hypergastrinemia (44). These results indicate that histamine is not essentially required for differentiation of progenitor stem cells to parietal, ECL, or other endocrine cells but is required to maintain normal gastric mucosal architecture and population with aging.

It is of note that, in addition to the pathological changes mentioned above, hypoalbuminemia was observed in H2R-KO mice. This finding is considered the hallmark of Menetrier’s disease (7, 33, 55) and is thought to result from albumin loss from cystic dilatation of the gastric mucosa (32, 48). Accordingly, we postulated that abnormalities in H2R function lie at the heart of the pathogenesis of the disease (44). We expected similar pathological changes in HDC-KO mice, because we assumed that a lack of histamine (HDC-KO) might be similar to deletion of gastric mucosal H2R (H2R-KO). However, the present study demonstrated that there was no difference in serum albumin levels for HDC-KO and WT mice. In addition, gastric hyperplastic mucosa was much milder in HDC-KO

Fig. 2. A: histamine levels in 6-mo-old WT and histidine decarboxylase-deficient (HDC-KO) mice (A). Time course changes in intragastric pH (B), stomach weight (C), and serum gastrin (D) and albumin levels (E) in WT (open circle or column) and HDC-KO (closed circle or column) mice. Values are means ± SE, n = 4–13. *Significant differences from WT mice of the same age, with P < 0.05.
mice compared with H₂R-KO mice (29, 44). Because there have been reports that other histamine receptors, i.e., H₁R (16, 38, 39) and H₃R (40), possess the potential to positively modulate gastric mucosal proliferation, it remains possible that histamine receptor signals might affect gastric mucosal hyperplasia in different manners. For instance, H₁R and H₃R might relate to promote hyperplasia, whereas H₂R relates to inhibit hyperplasia. This explanation could account for the mild hyperplastic mucosa and absence of albumin loss from the gastric mucosa observed in HDC-KO mice. In addition, the difference between the ligand and receptor deficiency, i.e., the observation that, whereas HDC-KO mice decreased basal acid secretion with increased intragastric pH (52), H₂R-KO mice have normal basal acid secretion (29, 44), would also support the explanation that other histamine receptors are involved in gastric mucosal functions.

In rodent gastric mucosa, ECL and mast cells represent the major histamine-producing cell (25, 46). Pharmacological analysis with α-FMH, which preferentially inhibits histamine synthesis in ECL cells, demonstrated that ECL cell-derived histamine predominantly regulates gastric acid secretion (2, 3, 5, 10, 13, 37) and mucosal morphology (2, 3, 5, 10, 13, 37). It has already been reported with different strains of mast cell-deficient mice, such as W/W⁺ (49) and C57B1/6J-mi/mi (50), that mast cells partially contribute to gastric acid secretion. Nonetheless, the role of mast cells for regulation of gastric mucosal morphology remains uncertain. The present study confirmed that gastric mucosal histamine levels in W/W⁺ mice were half the levels measured in +/+ mice, with no difference observed for intragastric pH and serum gastrin levels between the two groups. Similarly, gastric oxyntic mucosal morphology was normal in W/W⁺ mice even 1 yr after birth. These results indicate that mast cell-derived histamine does not play a critical role for maintenance of gastric mucosal architecture, probably due to presence of ECL-derived histamine.

To detect ECL cells with immunohistochemical analysis, anti-Cg A antibody was used instead of anti-HDC and anti-

![Fig. 3. Periodic acid Schiff staining of the gastric mucosa of 6-mo-old WT (A) and HDC-KO (B) mice (bar = 100 μm). Thickness of the oxyntic mucosa, pit region (open column; presence of surface mucous cells), and glandular basal region (filled column; presence of parietal, chief, and endocrine cells) in WT and HDC-KO mice (C). Note that the change in gastric mucosal thickness was most prominent in the glandular basal region compared with the pit region. Values are means ± SE, n = 7. Significant differences in the #mucosal thickness and *glandular base region for HDC-KO mice compared with WT mice (P < 0.05).](http://ajpgi.physiology.org/)

![Fig. 4. Time-course comparison of oxyntic mucosal thickness (A) and both chromogranin A (Cg A)-positive endocrine (B) and parietal cell counts (C) in WT (open circles) and HDC-KO (closed circles) mice. Sections were evaluated with hematoxylin and eosin staining (A) and immunostaining. Three months after birth, all 3 parameters in HDC-KO mice were significantly increased compared with WT mice. Values are means ± SE, n = 6–8. *Significant differences from WT mice of the same age (P < 0.05).](http://ajpgi.physiology.org/)
histamine antibodies, because HDC-KO mice lack both the HDC protein and histamine. In the present study, numerous CgA-positive endocrine cells could be detected in the oxyntic mucosa of both WT and HDC-KO mice. In gastric mucosa, CgA and its secretory peptide, pancreastatin, are known to be stored in the secretory vesicles of all endocrine cells, such as ECL, somatostatin-containing D, and ghrelin-containing A-like cells, among others (15, 42). Percentage of endocrine cells for the above cell types in the gastric oxyntic mucosa was 60, 20, and 20%, respectively (11). To distinguish ECL cells from CgA-positive cells, we attempted immunostaining of somatostatin-positive D cells and found that gastric oxyntic mucosal D cell density was similar for HDC-KO and WT mice. Similarly, it has been reported that hypergastrinemia, induced by a 10-wk omeprazole treatment, resulted in increases in oxyntic mucosa HDC mRNA levels without increases in ghrelin mRNA or somatostatin mRNA levels (20). It was also demonstrated that CCK2R deficiency in mice did not affect the number or ultrastructure of either A-like or D cells in the oxyntic mucosa (11, 12). In addition, CgA-gene expression was found to be regulated by serum gastrin levels in ECL cells (9, 17, 51, 54), and selective activation of CgA-gene expression was observed in the corpus mucosa in response to gastrin (17). In consideration of such reports and the present study, it
remains most likely that the increase in Cg A-positive cells in HDC-KO mice predominantly resulted from an increase in ECL cells. However, these cells did not possess the characteristic features of ECL cells, i.e., HDC or histamine. Interestingly, using immunohistochemical and electron microscopic analysis, Chen et al. (11, 12) described in CCK2 R-KO mice, ECL-like cells that possess all of the characteristic features of ECL cells except the ability to produce histamine. Because HDC expression in ECL cells is under tight control by serum gastrin levels (4, 11, 12, 30, 31), it is reasonable that CCK2 R deficiency results in an inability to produce histamine in ECL cells. Consequently, it is possible that the ECL-like cells Chen et al. (11, 12) described represent CCK2 R-KO ECL cells, which appear to resemble the HDC-KO ECL cells in this study.

Elevation of intragastric pH, resulting from gastric acid suppression by anti-secretory drugs, such as proton pump inhibitors (34–36) or H2R antagonists (31, 38, 39), induces hypergastrinemia (34–36) as well as ECL and parietal cell hyperplasia. In the present study, HDC deficiency resulted in intragastric pH elevation, which led to a prolonged hypergastrinemic state, which lasted up to 9 mo after birth. Accordingly, to examine whether hypergastrinemia contributes to gastric hyperplastic changes in HDC mice, we compared the differences in gastric hyperplasia for omeprazole-treated WT and HDC-KO mice. Although serum gastrin levels were similar in both groups, ECL and parietal cell counts, as well as mucosal thickness, were much higher in HDC-KO mice compared with omeprazole-treated WT mice. In addition, ECL and parietal cell hyperplasia induced in HDC-KO mice was partially suppressed by YM022 treatment. These findings are partially consistent with the reports that gastric mucosal hyperplasia induced by proton-pump inhibitors was prevented by selective CCK2 R antagonists (8, 14, 22). Because gastrin is known to stimulate gastrointestinal mucosal growth (19, 53), it appears reasonable that ECL and parietal cell hyperplasia in HDC-KO mice results from hypergastrinemia. However, in gastrin-deficient mice, no difference in total oxyntic mucosal ECL cell counts immunostained by anti-Cg A or anti-vesicular monoamine transporter 2 (VMAT2) antibodies was observed compared with the WT mice (23). Similarly, in hypergastrinemic CCK2 R-KO mice, total pancreastatin- and VMAT2-positive ECL cell counts were unchanged compared with the WT mice (11, 12). These reports suggest that factor(s) other than gastrin might directly or indirectly participate in the development of ECL cell hyperplasia in HDC-KO mice. Further studies are needed to determine the true role played by gastrin for gastric ECL cell hyperplasia induced in hypergastrinemia.

In conclusion, the present study demonstrated with HDC-KO and W/W* mice that ECL cell-derived histamine, as opposed to mast cell-derived histamine, plays a role in gastric mucosal morphology regulation. The HDC-KO mice model provides important information for better characterization of the complicated regulation of gastric morphological homeostasis.

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