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Pleotropic Effects of Proton Pump Inhibitors
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Gastric Epithelial Cell Modality and Proton Pump Inhibitor

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Summary **Proton pump inhibitors (PPIs) are now commonly used for the treatment of acid related diseases such as peptic ulcer and reflux esophagitis. Because of their ability to produce direct inhibition of the proton pump, PPIs provide more sustained increase of the gastric pH than H_2-receptor (H_2R) antagonists. Diverse reports have been published on gastric epithelial cell modality associated with PPI treatment both in animal models and clinical settings. The present review summarizes the recent accumulated evidence on gastric epithelial cell modality associated with PPI treatment, including the formation of gastric carcinoid tumors and fundic gland polyps, and the development of gastric mucosal atrophy. Long-term PPI treatment has been reported to cause enlargement of the parietal cells and enterochromaffin-like cells, and to decrease the number of chief cells without affecting A-like cell. Although the development of gastric carcinoid tumors after chronic PPI treatment has been reported in animal studies, no such occurrences have been demonstrated in humans. The effect of PPIs on the formation of fundic gland polyps and the development of atrophic gastritis should be investigated in future studies.**

Key Words: **proton pump inhibitor, gastric fundic gland, pariental cell, chief cell, ghrelin**

Introduction

Gastric acid in the stomach facilitates the digestion of protein and also protects against bacterial overgrowth and enteric infections. Gastric acid secretion is stimulated by histamine, gastrin or acetylcholine, mediated via the basolateral surface receptors on the parietal cells. Proton pump inhibitors (PPIs) inhibit H^+, K^+-adenosine triphosphatase (H^+, K^+-ATPase) in the parietal cells, which is involved in the final step of gastric acid secretion. The enzyme is composed of two subunits, a 114-kDa alpha-subunit and a 35-kDa beta-subunit [*1*, *2*]. PPIs are converted to tetracyclic sulfonamides which bind with the cysteine residues in the alpha subunit of the gastric H^+, K^+-ATPase. Besancon *et al.* reported that the common binding sites of PPIs is the cysteine residue at position 813 in the alpha subunit of the gastric H^+, K^+-ATPase (Fig. 1) [*3*]. As well as gastric parietal cells, Nakamura *et al.* reported PPI uptake sites have been seen in *Helicobacter pylori* (*H. pylori*), colonic epithelial cells, inflammatory cells, peripheral autonomic nerves and ECL cells [*4*].

Since PPIs produce histamine, gastrin or acetylcholine-independent inhibition of acid secretion, they provide more

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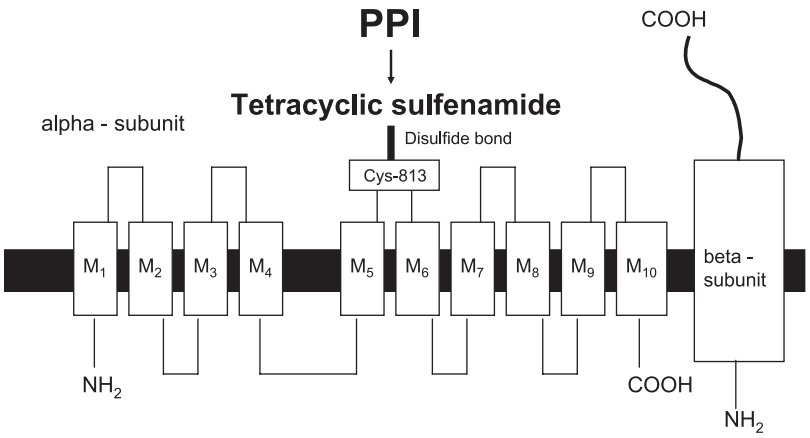

Fig. 1. Scheme of reaction of PPI and H^+, K^+-ATPase. PPI convert to tetracyclic sulfonamide and react with cysteine813 in the alpha subunit of the gastric H^+, K^+-ATPase.

sustained increase of the gastric pH than H_2-receptor (H_2R) antagonists [*5*]. In Japan, lansoprazole, omeprazole and rabeprazole are officially approved for the treatment of peptic ulcer disease, gastro-esophageal reflux disease (GERD) and *H. pylori* infection.

The gastric fundic glands are composed of several types of epithelial cells, such as pit cells, mucous-neck cells, chief cells, parietal cells, and endocrine cells such as entero-chromaffin-like (ECL) cells, A-like cells, somatostatin-producing D cells and gastrin producing G cells (Fig. 2). The epithelial cells are organized in tubular units that contain stem cells somewhere halfway up their length, in the isthmus zone. Pit cells migrate up from the isthmus towards the gastric lumen [*6*], mucous neck cells migrate down towards the base of the glands, where they transdifferentiate into chief cells [*7*], and parietal cells and endocrine cells migrate towards the gastric lumen and the glands in rodents [*8*, *9*]. PPI treatment reportedly affects the modality of these cells.

The present review is aimed at summarizing the information available about the effects of PPI treatment on the gastric epithelial cell modality.

Changes in Parietal Cells Induced by PPI Treatment

The apical surface of the gastric active parietal cells is greatly expanded during maximal acid secretion, as compared with that of the resting (inactive) parietal cells [*10*]. While cimetidine prevented this morphological transition of the parietal cells, omeprazole failed to prevent such transition during histamine stimulation [*11*]. In the last-mentioned report, administration of omeprazole caused vacuolation in approximately 27% of all the parietal cells [*11*], a phenomenon that was not seen in the parietal cells of the control animals treated with histamine alone and seen only very rarely in the parietal cells of the cimetidine-treated animals. Ultrastructural examination revealed the vacuoles

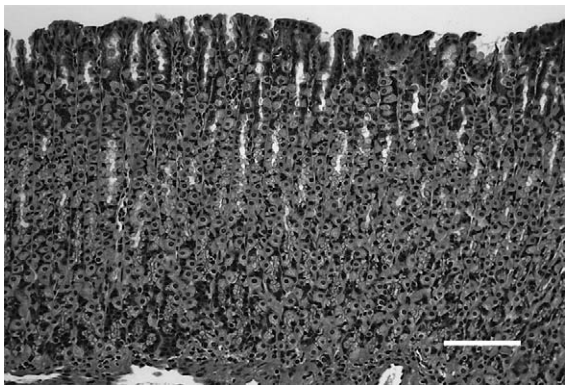

Fig. 2. Hematoxylin Eosin staining of gastric fundic gland of mouse. Scale bar indicates 100 μm.

may have originated from the secretory canaliculi of the parietal cells. In another study, the alpha subunit of gastric H^+, K^+-ATPase deficient mice showed characteristic parietal cells with cytoplasmic dilations and large cystic formations lined by a single layer of a low cuboidal epithelium [*12*].

KCNQ1 is a K^+ channel, mutation of which has been reported in cases with the cardiac long QT syndrome. KCNQ1 has been shown to be localized in the tubulovesicles and apical membrane of the parietal cells and to be colocalized with H^+, K^+-ATPase in these cells [*13*]. KCNE2 was identified as the beta subunit of KCNQ1 [*14*]. KCNQ1 and KCNE2 mediate efflux of K^+ ions to balance the influx of K^+ ions influx through the gastric H^+, K^+-ATPase. Interestingly, KCNQ1-deficient mice [*15*], KCNE2- deficient mice [*16*], as well as the beta subunit of the gastric H^+, K^+-ATPase deficient mice exhibited achlorhydria and vacuolization of the gastric parietal cells. Since the beta subunit of the gastric H^+, K^+-ATPase and gastrin double deficient mice did not exhibit such hyperplasia [*17*], it is speculated that such vacuolization might be attributable to secondary hyper-

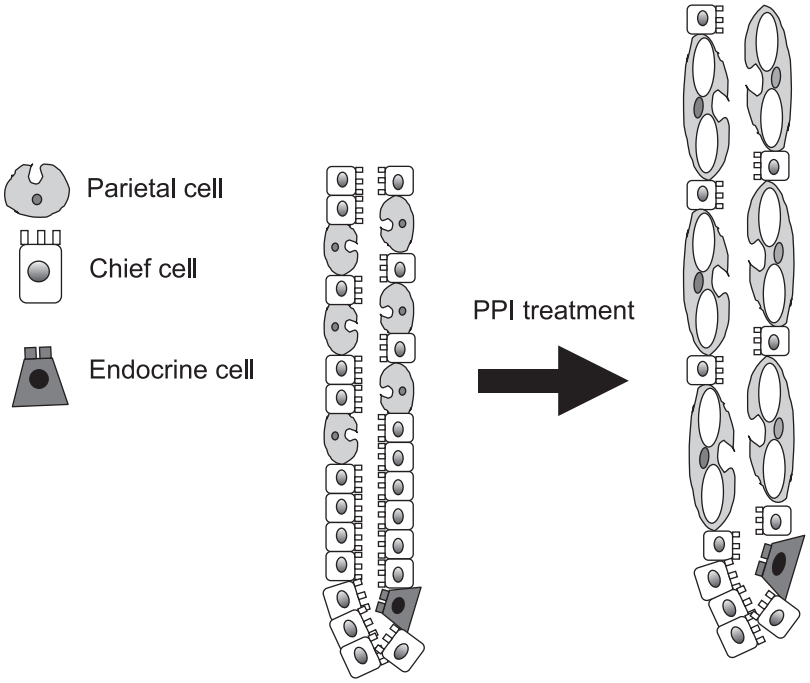

Fig. 3. Scheme of changes of gastric epithelial cell in the bottom of gastric gland by PPI treatment. PPI treatment caused enlargement of parietal cell and ECL cell, it decreased number of chief cells. Then, gastric gland became hyperplastic.

gastrinemia.

However, no significant changes of the parietal cell number or mucosal thickness were observed after short-term (2–6 weeks) omeprazole treatment in a human study [*18*]. On the other hand, Driman *et al.* [*19*] reported observing enlarged parietal cells with luminal bulges of cytoplasm, expanded tubulovesicles, and poorly developed secretory canaliculi after omeprazole treatment for longer than 12 months in a human study. Although the ultrastructural findings were dissimilar to those in the animal studies reported previously, this report does suggest that pathological changes of the parietal cells may be encountered after long-term PPI treatment. In conclusion, parietal cell enlargement has been reported following long-term PPI treatment in both animal and human studies (Fig. 3).

Changes in Chief Cells Induced by PPI Treatment

Sonic hedgehog (Shh) is a morphogen involved in many aspects of patterning of the gut during embryogenesis and in gastric fundic gland homeostasis in the adult [*20*]. Prolonged colonization by *H. pylori* has been reported to cause extension of the inflammation from the antrum to the corpus of the stomach, with loss of Shh expression which correlated with the loss of parietal cells [*21*, *22*]. To clarify the expression of Shh in parietal cell dysfunction not associated with inflammation, we used H_2R-deficient (H_2R-null) mice and an acid exposure model [*23*]. To study the effects of acid exposure, HCl solution was administered to the animals. The H_2R-null mice exhibited higher gastric pH, reduced Shh expression and impaired mucous neck-to-zymogenic cell differentiation. Furthermore, the expression level of Shh increased in the presence of gastric acid and showed a significant correlation with the gastric surface pH. These results suggest that suppressed gastric acid secretion alone may be sufficient to down-regulate Shh expression.

Kakei *et al.* [*24*] reported that 4 weeks treatment with omeprazole induced a marked decrease in the number of chief cells in the gastric mucosa with a concomitant increase in the number of immature pepsinogen-producing cells expressing class III mucin. These changes were associated with decrease to 60% and 10% of the control values in the mucosal levels of pepsinogen and its mRNA, respectively. Moreover, cell proliferation assays have revealed that the percentage of bromodeoxyuridine-labeled cells was increased by omeprazole. These alterations were reversed by discontinuation of the omeprazole treatment, suggesting that omeprazole treatment for 4 weeks induced a reversible change in the cell proliferation and de-differentiation of the gastric epithelial cells.

Changes in the Endocrine Cells Associated with PPI Treatment

Endocrine cells in the oxyntic mucosa are composed of ECL, D, enterochromaffin (EC), and A-like cells, as identi-

fied based on ultrastructural and immunohistochemical criteria [*25*].The relative percentages of these four cells in the human oxyntic glands are 30% for ECL cells, 20% for A-like cells, 22% for D cells, and 7% for EC cells [*26*]. D cells which produce somatostatin are located mainly in the pyloric antrum.

ECL cells have been reported to increase in size after 2 weeks of omeprazole treatment in rodents [*27*]. Lamberts *et al.* [*28*] reported the doubling of the mean argyrophil cell density after long-term (6–84) omeprazole treatment in patients with gastric ulcer. Eissele *et al.* [*29*] reported a statistically significant increase in the fundic gland argyrophil cell density after long-term (up to 5 years) lansoprazole treatment in patients with peptic disorders. In their paper, they reported detecting argyrophil cell hyperplasia in 2.6% of the patients before lansoprazole treatment and in 29.2% of the patients after long-term lansoprazole treatment. We previously reported the pH-independent effects of PPI such as lansoprazole on cell restitution *in vitro*; treatment with lansoprazole significantly promoted the cell restitution rate after wounding, while the addition of an MEK inhibitor significantly attenuated the cell restitution rate in the lansoprazole groups, suggesting that the mechanism of cell proliferation and migration promoted by lansoprazole might involve the activation of p44/p42 MAPK [*30*]. Such hyperplasia might be attributable to promoted cell proliferation.

In 1983, all of the omeprazole studies in humans were stopped because rodents given omeprazole developed gastric endocrine cell hyperplasia and carcinoid tumors [*31*]. Maton *et al.* reported that none of their patients with Zollinger-Ellison syndrome who were administered omeprazole for up to 3 years developed any significant changes in the percentage of argyrophil cells, carcinoid tumors, and changes in the serum concentrations of gastrin [*32*]. Jensen *et al.* reported that none of the 21 patients with Zollinger-Ellison syndrome who were administered lansoprazole for a mean of 31 months developed gastric carcinoid tumors [*33*]. These studies on patients with Zollinger-Ellison syndrome are of great significance in relation to the safety concerns of PPIs in terms of gastric carcinoid development.

A-like cells are major endocrine cells of the oxyntic mucosa of both rats and humans. A-like cells have been identified in the oxyntic mucosa based on ultrastructural and immunohistochemical criteria [*25*]. Recently, their hormonal product had been clarified as ghrelin [*34*]. Ghrelin, a peptide composed of 28 amino acids, has been shown to be a natural ligand of the growth hormone secretagogue receptor. Ghrelin is secreted from A-like cells in the gastric fundus [*35*]. Under physiological conditions, ghrelin stimulates not only GH release, but also food intake, cardiac out put, gastric motility and acid secretion [*36*]. Cui *et al.* [*37*] reported that omeprazole treatment for 11 weeks induced hypertrophy of the oxyntic mucosa with the hyperplasia of the ECL, but not A-like cells. Thus, PPI treatment might not affect the modality of A-like cells. On the other hand, *H. pylori* infection modified the dynamics of ghrelin [*38*, *39*].

Atrophic Gastritis and PPI Treatment

To evaluate whether acid suppression might increase the risk of atrophic gastritis, Kuipers *et al.* [*40*] compared patients with reflux esophagitis treated by fundoplication or omeprazole. In the cohort treated by fundoplication, none of the subjects showed development of atrophic gastritis. On the other hand, in the cohorts treated with omeprazole, development of atrophic gastritis was observed in 30.5% of the *H. pylori* infected patients. These findings suggest that omeprazole treatment might increase the risk of atrophic gastritis in patients with *H. pylori* infected reflux esophagitis. However, Lundell *et al.* [*41*] did not confirm these results. Then, Kuipers *et al.* [*42*] performed a prospective controlled trial to evaluate the effects of *H. pylori* eradication therapy. In their study, *H. pylori* eradication therapy eliminated gastric mucosal inflammation and induces regression of corpus gland atrophy. They concluded by recommending *H. pylori* eradication therapy in GERD patients receiving long-term acid suppressive therapy.

To clarify whether acid-suppressive therapy might promote corpus gastritis in patients with *H. pylori* infection, Uemura *et al.* [*43*] examined *H. pylori*-positive patients who were treated with either omeprazole alone or with omeprazole for primary therapy, followed by famotidine for maintenance therapy for 3 years in Japan. In their report, no increase in the frequency of endoscopically assessed mucosal atrophy was observed during the observation period. These differences might be attributable to the method of the assessment of atrophy [*43*] or racial differences.

Fundic-gland Type Polyps and PPI Treatment

Jalving *et al.* studied whether proton pump inhibitor use might lead to the development of fundic gland type polyps (FGPs) [*44*]. In their study, the presence of FGPs was assessed in patients receiving a PPI treatment. Among the 599 patients who participated, 322 patients were receiving PPI treatment, and 107 of these patients had fundic gland polyps. Long-term PPI treatment was associated with both a large proportional cystic area and parietal cell hyperplasia and protrusion. Vieth *et al.* retrospectively compared the frequency of FGPs in 2,251 patients without *H. pylori* infection who received PPI treatment (at least 4 weeks) with that in a control group of 28,096 patients without *H. pylori* infection and without PPI treatment. FGPs were identified at an identical frequency in both groups, indicating the unclear pathogenetic relationship between PPI treatment and FGPs [*45*].

Epilogue

Although, long-term PPI treatment was associated with enlargement of the parietal cell and ECL cells, the number of chief cells decreased and these drugs had no effect on the A-like cells. Although the development of gastric carcinoid tumors has been reported following chronic PPI treatment in animals, this has not been observed until now in humans. Clarification of the effect of PPIs on the formation of FGPs and the development of atrophic gastritis requires further investigation.

Abbreviations

PPIs, Proton pump inhibitors; H_2R, H_2-receptor; ECL cells, Enterochromaffin-like cells; H^+, K^+-ATPase, H^+, K^+-adenosine triphosphatase; GERD, gastro-esophageal reflux disease; *H. pylori*, *Helicobacter pylori*; Shh, Sonic hedgehog; EC, enterochromaffin; FGPs, fundic gland type polyps.

References

[1] Shull, G.E. and Lingrel, J.B.: Molecular cloning of the rat stomach (H+ + K+)-ATPase. *J. Biol. Chem.*, **261**, 16788–16791, 1986.

[2] Yeo, M., Kim, K.D., Chung, S.I., Moon, S.B., Song, S.K., and Hahm, B.K.: The Novel Acid Pump Antagonists for Anti-secretory Actions with Their Peculiar Applications Beyond Acid Suppression. *J. Clin. Biochem. Nutr.*, **38**, 1–8, 2006.

[3] Besancon, M., Simon, A., Sachs, G., and Shin, J.M.: Sites of reaction of the gastric H,K-ATPase with extracytoplasmic thiol reagents. *J. Biol. Chem.*, **272**, 22438–22446, 1997.

[4] Nakamura, M., Matsui, H., Serizawa, H., and Tsuchimoto, K.: Lansoprazole Novel Effector Sites Revealed by Autoradiography: Relation to Helicobacter pylori, Colon, Esophagus and Others. *J. Clin. Biochem. Nutr.*, **41**, 154–159, 2007.

[5] Mears, J.M. and Kaplan, B.: Proton pump inhibitors: new drugs and indications. *Am. Fam. Physician.*, **53**, 285–292, 1996.

[6] Karam, S.M. and Leblond, C.P.: Dynamics of epithelial cells in the corpus of the mouse stomach. II. Outward migration of pit cells. *Anat. Rec.*, **236**, 280–296, 1993.

[7] Karam, S.M. and Leblond, C.P.: Dynamics of epithelial cells in the corpus of the mouse stomach. III. Inward migration of neck cells followed by progressive transformation into zymogenic cells. *Anat. Rec.*, **236**, 297–313, 1993.

[8] Karam, S.M.: Dynamics of epithelial cells in the corpus of the mouse stomach. IV. Bidirectional migration of parietal cells ending in their gradual degeneration and loss. *Anat. Rec.*, **236**, 314–332, 1993.

[9] Karam, S.M. and Leblond, C.P.: Dynamics of epithelial cells in the corpus of the mouse stomach. V. Behavior of entero-endocrine and caveolated cells: general conclusions on cell kinetics in the oxyntic epithelium. *Anat. Rec.*, **236**, 333–340, 1993.

[10] Forte, J.G., Forte, T.M., Black, J.A., Okamoto, C., and Wolosin, J.M.: Correlation of parietal cell structure and function. *J. Clin. Gastroenterol.*, **5** Suppl 1, 17–27, 1983.

[11] Karasawa, H., Tani, N., and Miwa, T.: The effect of omeprazole on ultrastructural changes in gastric parietal cells. *Gastroenterol. Jpn.*, **23**, 1–8, 1988.

[12] Spicer, Z., Miller, M.L., Andringa, A., Riddle, T.M., Duffy, J.J., Doetschman, T., and Shull, G.E.: Stomachs of mice lacking the gastric H,K-ATPase alpha-subunit have achlorhydria, abnormal parietal cells, and ciliated metaplasia. *J. Biol. Chem.*, **275**, 21555–21565, 2000.

[13] Grahammer, F., Herling, A.W., Lang, H.J., Schmitt-Graff, A., Wittekindt, O.H., Nitschke, R., Bleich, M., Barhanin, J., and Warth, R.: The cardiac K+ channel KCNQ1 is essential for gastric acid secretion. *Gastroenterology*, **120**, 1363–1371, 2001.

[14] Heitzmann, D., Grahammer, F., von Hahn, T., Schmitt-Graff, A., Romeo, E., Nitschke, R., Gerlach, U., Lang, H.J., Verrey, F., Barhanin, J., and Warth, R.: Heteromeric KCNE2/KCNQ1 potassium channels in the luminal membrane of gastric parietal cells. *J. Physiol.*, **561**, 547–557, 2004.

[15] Elso, C.M., Lu, X., Culiat, C.T., Rutledge, J.C., Cacheiro, N.L., Generoso, W.M., and Stubbs, L.J.: Heightened susceptibility to chronic gastritis, hyperplasia and metaplasia in Kcnq1 mutant mice. *Hum. Mol. Genet.*, **13**, 2813–2821, 2004.

[16] Roepke, T.K., Anantharam, A., Kirchhoff, P., Busque, S.M., Young, J.B., Geibel, J.P., Lerner, D.J., and Abbott, G.W.: The KCNE2 potassium channel ancillary subunit is essential for gastric acid secretion. *J. Biol. Chem.*, **281**, 23740–23747, 2006.

[17] Franic, T.V., Judd, L.M., Robinson, D., Barrett, S.P., Scarff, K.L., Gleeson, P.A., Samuelson, L.C., and Van Driel, I.R.: Regulation of gastric epithelial cell development revealed in H(+)/K(+)-ATPase beta-subunit- and gastrin-deficient mice. *Am. J. Physiol. Gastrointest. Liver Physiol.*, **281**, G1502–1511, 2001.

[18] Helander, H.F., Simonsson, M., Sundler, F., Rutgersson, K., Helander, K.G., and Eriksson, S.: Histology of gastric biopsies from peptic ulcer patients before and after short-term treatment with omeprazole or H2-receptor antagonists. *Virchows Arch A Pathol. Anat. Histopathol.*, **417**, 305–309, 1990.

[19] Driman, D.K., Wright, C., Tougas, G., and Riddell, R.H.: Omeprazole produces parietal cell hypertrophy and hyperplasia in humans. *Dig. Dis. Sci.*, **41**, 2039–2047, 1996.

[20] van den Brink, G.R., Hardwick, J.C., Tytgat, G.N., Brink, M.A., Ten Kate, F.J., Van Deventer, S.J., and Peppelenbosch, M.P.: Sonic hedgehog regulates gastric gland morphogenesis in man and mouse. *Gastroenterology*, **121**, 317–328, 2001.

[21] Suzuki, H., Minegishi, Y., Nomoto, Y., Ota, T., Masaoka, T., van den Brink, G.R., and Hibi, T.: Down-regulation of a morphogen (sonic hedgehog) gradient in the gastric epithelium of Helicobacter pylori-infected Mongolian gerbils. *J. Pathol.*, **206**, 186–197, 2005.

[22] Nishizawa, T., Suzuki, H., Masaoka, T., Minegishi, Y., Iwasahi, E., and Hibi, T.: Helicobacter pylori eradication restored sonic hedgehog expression in the stomach. *Hepatogastroenterology*, **54**, 697–700, 2007.

[23] Minegishi, Y., Suzuki, H., Arakawa, M., Fukushima, Y., Masaoka, T., Ishikawa, T., Wright, N.A., and Hibi, T.: Reduced Shh expression in TFF2-overexpressing lesions of the gastric fundus under hypochlorhydric conditions. *J. Pathol.*, **213**, 161–169, 2007.

[24] Kakei, N., Ichinose, M., Tatematsu, M., Shimizu, M., Oka, M., Yahagi, N., Matsushima, M., Kurokawa, K., Yonezawa, S., Furihata, C., Shiokawa, K., Kageyama, T., Miki, K., and Fukamachi, H.: Effects of long-term omeprazole treatment on adult rat gastric mucosa—enhancement of the epithelial cell proliferation and suppression of its differentiation. *Biochem. Biophys. Res. Commun.*, **214**, 861–868, 1995.

[25] Sachs, G., Zeng, N., and Prinz, C.: Physiology of isolated gastric endocrine cells. *Annu. Rev. Physiol.*, **59**, 243–256, 1997.

[26] Simonsson, M., Eriksson, S., Hakanson, R., Lind, T., Lonroth, H., Lundell, L., O'Connor, D.T., and Sundler, F.: Endocrine cells in the human oxyntic mucosa. A histochemical study. *Scand. J. Gastroenterol.*, **23**, 1089–1099, 1988.

[27] Bottcher, G., Hakanson, R., Nilsson, G., Seensalu, R., and Sundler, F.: Effects of long-term hypergastrinaemia on the ultrastructure of enterochromaffin-like cells in the stomach of the rat, hamster and guinea pig. *Cell Tissue Res.*, **256**, 247–257, 1989.

[28] Lamberts, R., Creutzfeldt, W., Struber, H.G., Brunner, G., and Solcia, E.: Long-term omeprazole therapy in peptic ulcer disease: gastrin, endocrine cell growth, and gastritis. *Gastroenterology*, **104**, 1356–1370, 1993.

[29] Eissele, R., Brunner, G., Simon, B., Solcia, E., and Arnold, R.: Gastric mucosa during treatment with lansoprazole: Helicobacter pylori is a risk factor for argyrophil cell hyperplasia. *Gastroenterology*, **112**, 707–717, 1997.

[30] Suzuki, H., Masaoka, T., Minegishi, Y., Motosugi, Y., Miura, S., and Ishii, H.: Lansoprazole promotes gastric mucosal cell proliferation and migration by activating p44/p42 mitogen-activated protein kinase. *Wound Repair Regen.*, **12**, 93–99, 2004.

[31] Havu, N.: Enterochromaffin-like cell carcinoids of gastric mucosa in rats after life-long inhibition of gastric secretion. *Digestion*, **35** Suppl 1, 42–55, 1986.

[32] Maton, P.N., Lack, E.E., Collen, M.J., Cornelius, M.J., David, E., Gardner, J.D., and Jensen, R.T.: The effect of Zollinger-Ellison syndrome and omeprazole therapy on gastric oxyntic endocrine cells. *Gastroenterology*, **99**, 943–950, 1990.

[33] Jensen, R.T., Metz, D.C., Koviack, P.D., and Feigenbaum, K.M.: Prospective study of the long-term efficacy and safety of lansoprazole in patients with the Zollinger-Ellison syndrome. *Aliment Pharmacol. Ther.*, **7** Suppl 1, 41–50, discussion 61–66, 1993.

[34] Date, Y., Kojima, M., Hosoda, H., Sawaguchi, A., Mondal, M.S., Suganuma, T., Matsukura, S., Kangawa, K., and Nakazato, M.: Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. *Endocrinology*, **141**, 4255–4261, 2000.

[35] Kojima, M., Hosoda, H., Date, Y., Nakazato, M., Matsuo, H., and Kangawa, K.: Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature*, **402**, 656–660, 1999.

[36] Mori, M., Suzuki, H., Masaoka, T., Imaeda, H., Nomoto, Y., Hosoda, H., Nishizawa, T., Kangawa, K., and Hibi, T.: Intravenous ghrelin administration enhances gastric acid secretion—evaluation using wireless pH capsule. *Aliment Pharmacol. Ther.*, **24** Suppl 4, 96–103, 2006.

[37] Cui, G.L., Syversen, U., Zhao, C.M., Chen, D., and Waldum, H.L.: Long-term omeprazole treatment suppresses body weight gain and bone mineralization in young male rats. *Scand. J. Gastroenterol.*, **36**, 1011–1015, 2001.

[38] Suzuki, H., Masaoka, T., Hosoda, H., Ota, T., Minegishi, Y., Nomura, S., Kangawa, K., and Ishii, H.: *Helicobacter pylori* infection modifies gastric and plasma ghrelin dynamics in Mongolian gerbils. *Gut*, 187–194, 2004.

[39] Suzuki, H., Masaoka, T., Hosoda, H., Nomura, S., Ohara, T., Kangawa, K., Ishii, H., and Hibi, T.: Plasma ghrelin concentration correlates with the levels of serum pepsinogen I and pepsinogen I/II ratio – a possible novel and non-invasive marker for gastric atrophy. *Hepatogastroenterol.*, 1249–1254, 2004.

[40] Kuipers, E.J., Lundell, L., Klinkenberg-Knol, E.C., Havu, N., Festen, H.P., Liedman, B., Lamers, C.B., Jansen, J.B., Dalenback, J., Snel, P., Nelis, G.F., and Meuwissen, S.G.: Atrophic gastritis and Helicobacter pylori infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N. Engl. J. Med.*, **334**, 1018–1022, 1996.

[41] Lundell, L., Miettinen, P., Myrvold, H.E., Pedersen, S.A., Thor, K., Andersson, A., Hattlebakk, J., Havu, N., Janatuinen, E., Levander, K., Liedman, B., and Nystrom, P.: Lack of effect of acid suppression therapy on gastric atrophy. Nordic Gerd Study Group. *Gastroenterology*, **117**, 319–326, 1999.

[42] Kuipers, E.J., Nelis, G.F., Klinkenberg-Knol, E.C., Snel, P., Goldfain, D., Kolkman, J.J., Festen, H.P., Dent, J., Zeitoun, P., Havu, N., Lamm, M., and Walan, A.: Cure of Helicobacter pylori infection in patients with reflux oesophagitis treated with long term omeprazole reverses gastritis without exacerbation of reflux disease: results of a randomised controlled trial. *Gut*, **53**, 12–20, 2004.

[43] Uemura, N., Okamoto, S., Yamamoto, S., Matsumura, N., Yamaguchi, S., Mashiba, H., Sasaki, N., and Taniyama, K.: Changes in Helicobacter pylori-induced gastritis in the antrum and corpus during long-term acid-suppressive treatment in Japan. *Aliment Pharmacol. Ther.*, **14**, 1345–1352, 2000.

[44] Jalving, M., Koornstra, J.J., Wesseling, J., Boezen, H.M., S, D.E.J., and Kleibeuker, J.H.: Increased risk of fundic gland polyps during long-term proton pump inhibitor therapy. *Aliment Pharmacol. Ther.*, **24**, 1341–1348, 2006.

[45] Vieth, M. and Stolte, M.: Fundic gland polyps are not induced by proton pump inhibitor therapy. *Am. J. Clin. Pathol.*, **116**, 716–720, 2001.