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ORIGINAL ARTICLE

Acid Suppression by Proton Pump Inhibitors Enhances Aquaporin-4 and KCNQ1 Expression in Gastric Fundic Parietal Cells in Mouse

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Abstract
Background The widespread use of proton pump inhibitors (PPIs) is known to cause sporadic gastric fundic gland polyps (FGPs). Altered expression and localization of the water or ion transport proteins might contribute to the excess fluid secretion into the cystic lumen for the development of FGPs.
Aims We investigated the alteration of the murine gastric fundic mucosa after PPI treatment, and examined the expression of water channel aquaporin-4 (AQP4) and potassium channel KCNQ1, which are expressed only in the parietal cells in the gastric mucosa.
Methods Male 5-week-old C57BL/6J mice were administered lansoprazole (LPZ) by subcutaneous injection for 8 weeks. The expression of AQP4 and KCNQ1 were investigated by Western blotting, quantitative RT-PCR, and immunohistochemistry. The expression of mucin-6 (Muc6), pepsinogen, and sonic hedgehog (Shh) were also investigated as mucosal cell lineage markers.
Results Gastric mucosal hyperplasia with multiple cystic dilatations, exhibiting similar histological findings to the FGPs, was observed in the LPZ-treated mice. An increase in the number of AQP4-positive parietal cells and KCNQ1-positive parietal cells was observed. The extension of the distribution of AQP4-positive cells toward the surface of the fundic glands was also observed. The expression levels of AQP4 mRNA and protein were significantly enhanced. The expression of KCNQ1 mRNA was correlated with that of AQP4 mRNA in the LPZ-treated mice. Mucous neck-to-zymogenic cell lineage differentiation was delayed in association with decreased expression of Shh in the LPZ-treated mice.
Conclusions PPI administration increased the number of parietal cells with enhanced expression of AQP4 and KCNQ1.

Keywords Proton pump inhibitors · Aquaporins · Potassium channels · Fundic gland polyps

Introduction

Proton pump inhibitors (PPIs) strongly inhibit the function of H^+/K^+-ATPase in gastric parietal cells, causing profound suppression of acid secretion. The use of PPIs has become widespread for the treatment of peptic ulcer disease and gastroesophageal reflux disease [1]. Such widespread use of PPIs has recently come to be known to be associated with the formation of gastric sporadic fundic gland polyps (FGPs), particularly in patients with *Helicobacter pylori*-free stomachs [2, 3]. FGPs are the most common gastric polyps [4]. A recent study showed that the prevalence of gastric polyps in the esophagogastroduodenoscopy population was 6.4% in the USA, and 77% of these lesions were FGPs [5]. FGPs are defined as cystic dilatations of the oxyntic glands lined by variably flattened parietal and chief cells with or without foveolar

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