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The influence of pioglitazone on basal gastric acid secretion in omeprazole-treated rats

Wpływ pioglitazonu na wydzielanie podstawowe kwasu żołądkowego u szczurów leczonych omeprazolem

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated intracellular transcription factors that have been implicated in important biological processes such as inflammation, tissue remodelling and atherosclerosis. Emerging information also implies PPARs in cancerogenesis. PPARgamma, the best studied of the PPAR is known to be expressed in several cancers [8], and the treatment of these cancer cells with PPARgamma ligands often induces cell differentiation and apoptosis.

Gastrin plays an important role in the gastric phase of acid secretion. Furthermore, accumulating evidence has suggested that gastrin has a trophic effect on gastric epithelial cells. In fact, ECL carcinoid tumors often develop in patients with hypergastrinemia, such as autoimmune gastritis and Zollinger-Ellison syndrome [9]. In addition to ECL cells, gastrin appears to have a growth-promoting effect on other gastric epithelial cells. Gastrin over expressing transgenic mice have been shown to have gastric mucosal hyperplasia [7]. The trophic effect of gastrin has also been demonstrated in mice by long-term administration of proton pump inhibitors [3]. It is known that long-term hypergastrinemia leads to gastric mucosal hypertrophy and may provoke gastric tumors. Formerly, we showed that proton pump inhibitor omeprazole (OM) (14mg/kg daily, i.p.) in 28 days evoked hyperplasia in gastric mucosa [10].

In this study, we attempted to elucidate the role of PPARgamma in gastric carcinogenesis and explored the possible use of synthetic PPARgamma ligand-pioglitazone as a chemopreventive agent for gastric mucosal hypertrophy, which leads to gastric cancer. We investigate the prophylactic action of agonist of PPARgamma pioglitazone on mucosal hypertrophy evoked by long-term hypergastrinemia.

MATERIAL AND METHODS

The study was carried out on 50 white rats. They were divided into three groups. The animals of the first (control) group were injected 0.2 ml H2O (i.p.). The rats of the second group were injected OM (14mg/kg, i.p.). The rats of the third group were injected the same dose of OM and pioglitazone (30mg/kg, per os). All drugs were injected during 28 days. The functional state of parietal cells and

gastric mucosal hypertrophy was evaluated by gastric acid output (BAO) [5]. BAO was determined 24 hours after the last injection in acute experiments under urethane anaesthesia (1.1 g/kg, i.p.) by the method of isolated stomach perfusion by Ghosh and Shild [4]. Also, in rats blood plasma, gastrin concentration was measured by radioimmunoassay method. The statistical evaluation was calculated by Student's t-test.

RESULTS

It was established that in 28 days of OM injection BAO (Fig. 1) and gastrin (Fig. 2) plasma levels were increased by 283.7% and 189.3% in comparison to control, accordingly. After 28 days of pioglitazone and OM treatment, BAO was diminished by 53.4% in comparison to rats after 28 days of OM injection. But pioglitazone did not influence augmentation of gastrin plasma level evoked by OM.

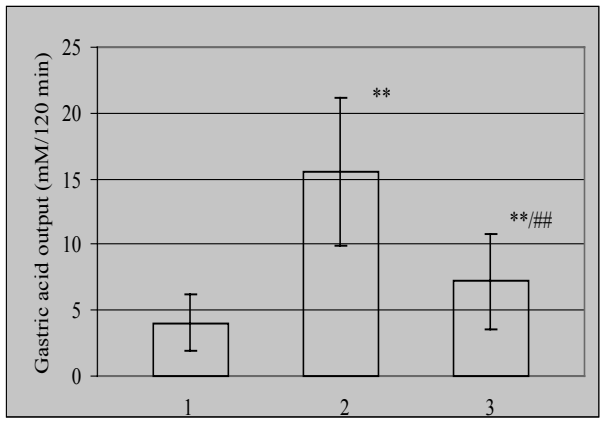

Fig. 1. Basal gastric acid secretion in rats after injection of omeprazole during 28 days (14 mg/kg) and joint injection of pioglitazone (30 mg/kg) and omeprazole, (M ± SD); 1 – control (n=26); 2 – omeprazole (n=6); 3 – omeprazole+pioglitazone (n=10) ** p<0.01, comparing to control; ## p<0.01, comparing to omeprazole

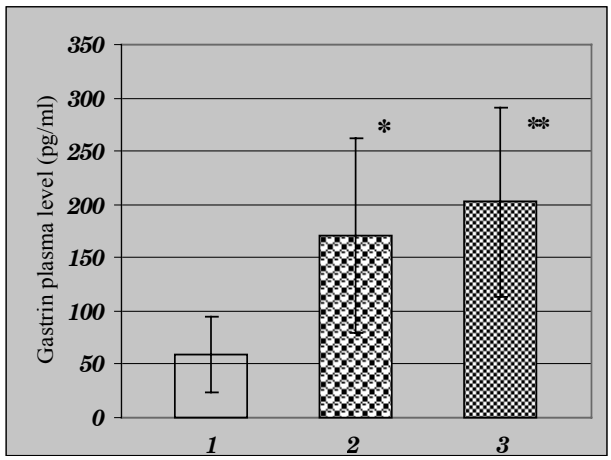

Fig. 2. The concentration of gastrin in plasma (pg/ml), (M ± SD); 1 – control; 2 – omeprazole; 3 – omeprazole+pioglitazone, * p<0.05, ** p<0.01 comparing to control

DISCUSSION

We first demonstrated that PPAR-gamma ligand pioglitazone prevented mucosal hypertrophy because BAO in rats after simultaneous treatment of OM and pioglitazone was lower in comparison with rats after injection of only OM. We assumed that it is connected the with the properties of pioglitazone to evoke cell differentiation. This conclusion is consistent with the works of other investigators. PPAR-gamma induces *in vitro* and *in vivo* terminal differentiation of human primary lyposarcoma cells characterized by accumulation of intracellular lipid, and induction of adipocyte-specific genes [1]. In human breast cancer, ligand activation of this receptor causes extensive lipid accumulation and changes in breast epithelial gene expression associated with a more differentiated, less malignant state [6]. In pancreatic cancer cell lines, PPAR-gamma agonists induce up-regulation of several differention markers such as carcinoembryonic antigen, E- cadherin and alkaline phosphatase [2]. Our data allow us to conclude that 1) hypergastrinemia evoked by OM leads to the general hyperplasia and hyperplastic mucosa has an increased capacity to produce acid; 2) compensatory effect of pioglitazone on gastric acid secretion may indicate retardation of mucosal hypertrophy process evoked by hypergastrinemia. Thus, pioglitazone is a perspective effective chemopreventive agent for gastric cancer.

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SUMMARY

In the experiment on rats it was shown that a daily injection of omeprazole (14 mg/kg, i.p.) during 28 days evoked the increase of gastrin plasma level by 189.3% ($p<0.05$). As a result, gastric mucosal hypertrophy was developed. Therefore, we can see the rise of gastric acid output by 283.7% ($p<0.01$). In rats in 28 days of combined treatment of peroxisome proliferator-activated receptors ligand pioglitazone (30 mg/kg, i.p.) and omeprazole gastric acid output was diminished by 53.4% in comparison to rats after 28 days of isolated omeprazole injection. But pioglitazone did not influence augmentation of gastrin plasma level evoked by omeprazole. Thus, the compensatory effect of pioglitazone on gastric acid secretion may indicate retardation of mucosal hypertrophy process evoked by hypergastrinemia.

STRESZCZENIE

W doświadczeniu na szczurach wykazano, że codzienne podawanie omeprazolu (14 mg/kg, i.p.) przez okres 28 dni powodowało wzrost poziomów osoczowych gastryny o 189,3 % ($p < 0,05$). W efekcie tego dochodziło do rozwoju hipertrofii śluzówki żołądka, co skutkowało wzrostem wydzielania kwasu żołądkowego o 283,7 % ($p < 0,01$). W grupie szczurów, którym przez okres 28 dni podawano pioglitazon i omeprazol, wydzielanie kwasu żołądkowego była o 53,4 % niższe niż u szczurów otrzymujących wyłącznie omeprazol. Pioglitazon nie wpływał jednakże na podwyższone stężenie gastryny w osoczu wywołane podawaniem omeprazolu. Kompensacyjny efekt pioglitazonu na wydzielanie kwasu żołądkowego może wskazywać na opóźnienie rozwoju procesu hipertrofii śluzówki żołądka wywołane przez hipergastrynemię.