Endocrinology of Duodenal Ulcer

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Several gastrointestinal peptides with proven or suggested endocrine or paracrine functions influence gastric acid secretion, gastrointestinal motility, and mucosal blood flow. Increased or decreased release of such factors could participate in the pathogenesis of duodenal ulcer disease by inducing increased gastric acid concentration in the duodenal bulb. To date, increased stimulation of parietal cells by gastrin has been demonstrated only in patients with gastrinoma, G-cell hyperplasia, gastric outlet obstruction, hyperparathyroidism, excluded antrum, and short bowel syndrome, but not in the usual duodenal ulcer disease. Also, a defective inhibition of parietal cell function by endocrine or paracrine factors, such as gastric inhibitory polypeptide, secretin, somatostatin and vasoactive intestinal polypeptide, seems not to exist in patients with duodenal ulcer disease. However, as long as the physiology of gastrointestinal peptides in gastric secretion and motility is not understood, a possible role of these factors in the pathogenesis of simple duodenal ulcer disease cannot be excluded.

Increased gastric acid and pepsin concentration in the duodenal bulb are believed to play an important role in the pathogenesis of duodenal ulcer. Increased duodenal acid and pepsin concentration may arise from gastric hypersecretion, an abnormally rapid rate of gastric emptying, and/or defective neutralization of acid in the duodenal bulb [1]. Secretion and motility are regulated by multiple neural and humoral (endocrine and paracrine) factors. Endocrine factors involved in the control of gastric acid secretion and their possible role in the pathogenesis of acid hypersecretion are summarized in Table 1. In discussing the significance of endocrine abnormalities in duodenal ulcer disease, we make no attempt to explain the pathogenesis of duodenal ulcer (DU) by these factors alone, at least not for the majority of DU patients.

Hypergastrinemia

Autonomous Gastrin Hypersecretion

The Zollinger-Ellison syndrome (ZES) (pancreatic or duodenal gastrinoma) is a classic example of the significant role that gastrin hypersecretion plays in the pathogenesis of ulcer disease [2-4]. Figure 1 demonstrates the gastrin concentrations in serum and tissue extracts from 15 ZES patients compared to that of DU patients and controls. In contrast to the rather uniform finding of extremely high serum gastrin levels in ZES patients, amounting to 20-10,000-fold higher levels than in controls and DU patients, the tumor gastrin concentration varied greatly. It rarely exceeded that of normal antral mucosa, which consists only of approximately 1-3% G cells. From this, it can be concluded that gastrinoma cells have a reduced storage capacity.

Sephadex® G-50 gel filtration studies of sera and gastrinoma tissues demonstrate that gastrin from
Table 1. Possible role of gastrointestinal hormones in gastric acid hypersecretion.

1. Increased stimulation of parietal cells by gastrin
   1.1. Autonomous gastrin hypersecretion
       Gastrinoma
       G-cell hyperplasia
   1.2. Increased G-cell stimulation
       Hyperparathyroidism
       Stomach outlet obstruction
   1.3. Defective inhibition of gastrin release
       Excluded antrum
       Short bowel syndrome
       Somatostatin deficiency
   1.4. Hyperactivity of antral G cells (elevated neural tone)

2. Defective inhibition of parietal cell function
   2.1. Endocrine factors
       Defective secretion of secretin, GIP, VIP, enterogastrone
   2.2. Paracrine factors
       Somatostatin and VIP deficiency

3. Defective neutralization of acid in the duodenal bulb
   3.1. Pancreatic bicarbonate deficiency (secretin, VIP)
   3.2. Rapid stomach emptying (motilin)

gastrinomas, as from the normal antral and duodenal mucosa, consists of different molecular forms. However, no obvious relationship could be found between the distribution of immunoreactive gastrin (IRG) components in the tumor tissues and sera of the individual gastrinoma patients. Also, no relationship existed to the morphologic data or the origin of the tumor (pancreatic or duodenal) [4].

A paradoxically rapid increase of serum gastrin occurs in ZES patients after intravenous injection of secretin [5] and glucagon [6, 7], and an exaggerated increase occurs after calcium infusion [8]. By means of these tests, gastrinoma patients can be separated from DU patients. Figure 2 shows the distribution of serum gastrin components G-45 (Rehfeld's Component I-C1), G-34, and G-17 in 6 gastrinoma patients before, and 2 and 45 minutes after, the intravenous injection of 75 KU of secretin. All 3 components are released into the blood circulation, but their relative abundance after stimulation was not related to the fasting pattern or the relative abundance of G-34 and G-17 in the tumor.

It has been claimed that intractable DU disease can be due to antral G-cell hyperplasia without pancreatic or duodenal gastrinoma [9, 10]. The existence of this entity seems to be even more rare than gastrinoma. Patients with G-cell hyperplasia respond normally to a test meal but, different from gastrinoma patients, serum gastrin was reported to increase less than 100% after secretin or calcium infusion, or even to decrease after secretin [10, 11]. Basal serum gastrin is less elevated than in the majority of gastrinoma patients. In Fig. 3, gastrin response to secretin is shown in 5 patients with hypergastrinemia and gastric acid hypersecretion of different origin. Patient M6. suffered from a proven duodenal gastrinoma, patient Ge. from an "excluded antrum" after Billroth II resection, and patients Du., Su., and Ha. from antral G-cell hyperplasia. The diagnosis of antral G-cell hyperplasia was proven by immunohistologic demonstration of marked G-cell hyperplasia in antral biopsies. Distribution of antral G cells in a normogastrinemic DU patient (Fig. 4A) may be compared with distribution in a patient with G-cell hyperplasia (Fig. 4B). In patients Ge., Ha., and Du., basal gastrin levels decreased to undetectable values after removal of the "excluded antrum" or by antrectomy. Patient Su. improved during long-term treatment with cimetidine. Only in the gastrinoma patient did gastrin increase by more than 100% after injection of 75 KU of secretin. The number of G cells, the antral gastrin concentration, and the basal serum gastrin of patients with G-cell hyperplasia are summarized in Table 2 and compared to those of controls, DU pa-