ABSTRACT

Mucosal atrophy of the gastric antrum (type B atrophic gastritis) is generally accepted as predisposing to the development of the intestinal type of gastric cancer. Since bombesin stimulates gastrin release selectively from the antral mucosa, the response can be used as a marker for antral mucosal atrophy. In this study we have investigated bombesin-stimulated plasma gastrin responses in 21 patients with the intestinal type of gastric cancer and we have compared the results with 12 patients with the diffuse type of gastric cancer, 17 patients with benign gastric ulcer, and 30 dyspeptic patients without endoscopic or histological abnormalities. Gastrin concentrations were also measured in extracts of antral biopsies. Basal plasma gastrin concentrations were not significantly different. In contrast, patients with the intestinal type of gastric cancer had a significantly lower plasma gastrin response to bombesin than did the normal subjects ($P < 0.01$) and patients with the diffuse type of gastric cancer ($P < 0.05$), but the result was not significantly different from that of the gastric ulcer patients. The antral gastrin content of the patients with the intestinal type of gastric cancer was significantly lower than in controls ($P < 0.005$), the patients with the diffuse type of gastric cancer ($P < 0.05$), and those with gastric ulcer ($P < 0.05$).

It is concluded that patients with the intestinal type of gastric cancer have, in contrast to those with the diffuse type of gastric cancer, an abnormally low plasma gastrin response to bombesin. This low response is due to a reduced gastrin content of the antral mucosa.

INTRODUCTION

Although the incidence of gastric cancer is decreasing in most western countries, the disease is still one of the most common malignancies. Unfortunately, in spite of this fall in incidence and in spite of more effective diagnostic techniques, the 5-year survival rate is still very low, between 5 and 20% (1). Most of the patients are at the time of diagnosis beyond cure, and they will eventually die from the tumor in spite of the most extensive application of available therapy. To improve the survival rate of this disease early diagnosis by follow-up of identified high risk patients is needed (2).

It is generally accepted that injury to the gastric mucosa leads to gastritis and mucosal atrophy, which is considered to be an essential step in gastric carcinogenesis (2–4). Epidemiological, clinical, and histological studies point especially to the so-called type B atrophic gastritis resulting in antral mucosal atrophy (2, 5), as a major risk factor for gastric cancer (5–12). Histologically, gastric cancer can be divided into two types (13), the intestinal and the diffuse type, and each of them seems to have a different etiopathogenetic background and a different biological behavior. The majority of gastric carcinomas arise in the antrum and it is generally accepted that the intestinal type of gastric carcinoma develops on the basis of an atrophic gastric mucosa (6, 10, 14–16). Until recently, absence of a marker for the severity and extent of type B atrophic gastritis has precluded systematic studies in high risk patients. We have recently demonstrated that the serum gastrin response to bombesin can be used to quantify the severity and extent of atrophy of the antral mucosa (17).

The purpose of this study was to determine whether patients with the intestinal type of gastric cancer have a reduced plasma gastrin secretion during infusion of bombesin, when compared with patients with the diffuse type of gastric cancer, with gastric ulcer, and control subjects. In addition, the plasma gastrin response to bombesin was related to the gastrin content of the antral mucosa.

MATERIALS AND METHODS

The plasma gastrin response to bombesin and the antral mucosal gastrin concentration were measured in 21 (15 male, 6 female) patients with the intestinal type of gastric cancer (mean age, 60 years; range, 46–84 years), 12 patients (8 male, 4 female) with the diffuse type of gastric cancer (mean age, 57 years; range, 24–71 years), 17 patients (12 male, 5 female) with a benign gastric ulcer (mean age, 55 years; range, 36–75 years), and 30 dyspeptic control patients (20 male, 10 female) without endoscopic or histological abnormalities (mean age, 51 years; range, 29–72 years).

The patients were studied after an overnight fast. Synthetic bombesin-14 (UCB, Brussels, Belgium) was infused in a dose of 60 pmol/kg over 20 min (18, 19). Blood samples for gastrin measurement were obtained at −5, 0, 5, 10, 15, and 20 min. Plasma gastrin was measured by a sensitive and specific radioimmunoassay as described elsewhere (18, 19). At endoscopy, at least 3 antral biopsies (total weight between 15 and 25 mg) were taken from the greater curvature of the antrum between 1 and 2 cm from the pylorus. In case tumor or ulcer was present in the prepyloric area, biopsies were taken from the antral mucosa at least 1 cm from the lesion. The antral biopsies were immediately frozen until processing. Gastrin was extracted from the biopsies in 1 ml boiling water for 10 min. After homogenization and centrifugation ($5000 \times g$ for 10 min), the supernatant was frozen until measurement for gastrin by radioimmunoassay (18, 19). Results were expressed as nmol gastrin per G-antral mucosa.

Results are expressed as the median and range. Integrated plasma gastrin secretion during bombesin infusion was determined by calculating the area under the plasma concentration-time curve after subtraction of basal value. Wilcoxon’s rank sum test was used for statistical analysis. Correlations between integrated plasma gastrin secretion and antral gastrin content were analyzed by Spearman’s correlation test. Informed consent was obtained from all subjects studied and the protocol was approved by the local ethical committees.

RESULTS

Basal plasma gastrin concentrations were not significantly different (Fig. 1). Only 3 of the 33 (9%) gastric cancer patients (one intestinal and 2 diffuse types) and 3 of the 17 gastric ulcer patients (18%) had basal plasma gastrin concentrations below the lowest result in the normal subjects.
Infusion of bombesin increased plasma gastrin in all groups of patients studied. However, there were marked differences in the responses. As shown in Fig. 2, 10 of the 33 (30%) gastric cancer patients had an incremental plasma gastrin response to bombesin below the lowest result in the control group. Interestingly, 8 of these patients with such a reduced response were patients with the intestinal type of gastric cancer. In fact, the incremental plasma gastrin response to bombesin in the patients with the intestinal type of gastric cancer was significantly ($P < 0.05$) lower than in the normal controls, whereas the responses in the patients with the diffuse type of gastric cancer and those with gastric ulcer were not significantly different from the controls. Furthermore, the incremental plasma gastrin response to bombesin in the patients with the intestinal type of gastric cancer was lower than in the patients with the diffuse type of gastric cancer ($P = 0.05$).

Similar results were obtained when the integrated plasma gastrin response to bombesin was calculated (Fig. 3). The median integrated plasma gastrin secretion in patients with the intestinal type of gastric cancer was significantly lower than in the normal subjects ($P < 0.01$) and patients with the diffuse type of gastric cancer ($P < 0.05$) but was not significantly different from the gastric ulcer patients.

The antral gastrin content in extracts of antral biopsies are shown in Fig. 4. Seven of the 33 patients (21%) with gastric cancer had antral gastrin concentrations below the lowest result in the normal subjects; all 7 were suffering from the intestinal type of gastric cancer. The median antral gastrin concentration in patients with the intestinal type of gastric cancer was significantly lower than in controls ($P < 0.005$), the diffuse type of gastric cancer ($P < 0.05$), and the gastric ulcer patients ($P <$
0.05), whereas the antral gastrin content of the patients with the diffuse type of gastric cancer or benign gastric ulcer did not significantly differ from the normal controls.

There were significant correlations between the integrated plasma gastrin secretion during bombesin infusion and the antral gastrin content in patients with the intestinal type of gastric cancer \((r = 0.76; \ P < 0.001)\), with the diffuse type of gastric cancer \((n = 0.64; \ P < 0.02)\), with benign gastric ulcer \((r = 0.50; \ P < 0.02)\), but not in the control subjects \((r = -0.03; \ not\ significant)\).

**DISCUSSION**

This study shows that a reduced plasma gastrin response to infusion of bombesin is found in 30% of patients with gastric cancer. Interestingly, most of these abnormalities are confined to patients with the intestinal type of gastric cancer. In fact, patients with the intestinal type of gastric cancer had a significantly lower plasma gastrin response to bombesin than did normal subjects and patients with the diffuse type of gastric cancer. This finding indicates that, in contrast to the other patients studied, patients with the intestinal type of gastric cancer often have type B atrophic gastritis, further pointing to a relationship between type B atrophic gastritis and this form of gastric cancer. The fact that the bombesin-stimulated gastrin secretion in patients with benign gastric ulcer was not significantly different from the patients with the intestinal type of gastric cancer may appear remarkable, but it is well known that a benign gastric ulcer is often accompanied by type B atrophic gastritis and has therefore been considered as a risk factor for the intestinal type of gastric cancer.

Several studies suggest that the incidence of type B atrophic gastritis is relatively high, especially in elderly people \((6, 7)\). The majority of gastric cancers are of the intestinal type \((10, 15, 20–23)\), which develops on the basis of mucosal atrophy of the antrum as a result of type B atrophic gastritis \((13, 15, 24)\). The diagnosis of atrophy of the antral mucosa is usually made by histological examination of endoscopic biopsies. However, the endoscopic diagnosis of atrophy of the antral mucosa and intestinal metaplasia is difficult, even when visualization is improved by *in vivo* staining \((25)\). Moreover, the patchy distribution of antral mucosal atrophy and intestinal metaplasia prevents quantification of the severity and extent of mucosal atrophy in endoscopic biopsies.

Previously, low numbers of \(\text{G}-\) (gastrin) cells have been found in the antral mucosa of achlorhydric patients in whom the mucosal atrophy has extended to the antrum \((26)\). This finding suggests that the plasma gastrin response to bombesin, a selective stimulus of antral gastrin secretion \((18, 19, 27)\), can be used to determine the severity and extent of antral mucosal atrophy. In fact, we have demonstrated that the “bombesin test” is useful for accurately diagnosing and quantifying atrophy of the antral mucosa \((17)\). As confirmed in the present study, basal plasma gastrin concentrations cannot reliably indicate the presence of type B atrophic gastritis. Another finding supporting the reliability of the gastrin response to bombesin for determining atrophy of the antral mucosa was the significant correlation between the plasma gastrin secretion and the antral gastrin contents in patients with the intestinal type of gastric cancer.

In conclusion, the present study shows that, in contrast to patients with the diffuse type of gastric cancer, the majority of patients with the intestinal type of gastric cancer have a low plasma gastrin response to bombesin. This low response is not caused by cancerous involvement of the antrum but to a low gastrin content of the antral mucosa, indicating atrophy of the antral mucosa. This finding suggests that the plasma gastrin response to bombesin is of great potential value in identifying patients with an increased risk for gastric cancer.

**REFERENCES**

Plasma Gastrin Responses to Bombesin and Antral Gastrin Concentrations in Patients with the Intestinal Type of Gastric Cancer


Updated version  Access the most recent version of this article at:  
http://cancerres.aacrjournals.org/content/48/8/2296

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.