Ovarian Cancers Express and Process Progastrin

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ABSTRACT

Gastrin synthesis in ovarian tumors has been described in a few isolated cases associated with the Zollinger-Ellison syndrome. Consequently, ovarian gastrin synthesis has been considered exceptional. In order to evaluate whether expression of gastrin in ovarian tumors indeed is rare, we examined the expression and processing of progastrin in 16 malignant and 5 benign ovarian tumors and 4 normal postmenopausal ovaria. Using a library of sequence specific radioimmunoassays, cleavage by processing, and chromatography, we found that one-half of the malignant tumors expressed significant concentrations of amidated gastrins (6.7 ± 2.7 (SEM) pmol/g, range, 1.4–20.0 pmol/g, n = 7). The concentrations of glycine-extended gastrins and progastrins were low (0.25 ± 0.03 and 1.4 ± 0.4 pmol/g, respectively) but higher than in controls and benign tumors. Chromatography showed that the majority of the bioactive gastrins was unsulfated gastrin-17. The other half of the malignant tumors expressed glycine-extended gastrins and progastrins (0.2 ± 0.03 and 0.6 ± 0.1 pmol/g; n = 9), but the amidation of the peptides was impaired (0.1 ± 0.03 pmol/g). Low concentrations of glycine-extended gastrins and progastrins were detected in the normal ovarian tissues (0.2 ± 0.05 pmol/g tissue and 0.2 ± 0.06 pmol/g, respectively, n = 4) and in the benign tumors (0.1 ± 0.02 pmol/g and 0.5 ± 0.03 pmol/g; n = 5). Amidated gastrins were undetectable, except in low amounts in a single benign tumor (0.2 pmol/g tissue). The results show that postmenopausal ovaria and neoplastic ovarian tissues express the gastrin gene at peptide level. The synthesis and processing of progastrin increase considerably in malignant tumors.

INTRODUCTION

Progastrin matures to bioactive peptides by proteolysis at mono- and dibasic cleavage sites and by amino acid derivatizations (sulfation, phosphorylation, and amidation). Of these, phenylalanine carboxyamidation is necessary for bioactivity [Fig. 1 (1)]. Bioactive gastrins stimulate gastric acid secretion and fundic mucosal growth (2, 3). Accordingly, gastrin producing tumors (gastrinomas) lead to recurrent peptic ulceration and hyperplasia of the fundic mucosa, i.e., the Zollinger-Ellison syndrome (4, 5).

By far most gastrinomas are located in pancreas or duodenum (6). During the last decades ten isolated cases of the Zollinger-Ellison syndrome due to gastrin secreting ovarian tumors have been reported (7–16). Although ovarian gastrin synthesis in amounts sufficient to develop a fulminating Zollinger-Ellison syndrome appears to be extremely rare, neuroendocrine cells have been demonstrated as a regular feature of mucinous ovarian cystadenocarcinomas. Some of these cells contained gastrin immunoreactivity (17, 18). This observation prompted us to investigate whether the synthesis of gastrin in ovarian tumors is a sporadic or a general phenomenon.

We have now measured the expression and processing of progastrin in ovarian tumors and normal postmenopausal ovaria using a library of sequence specific radioimmunoassays for human progastrin. We also measured other peptide systems (CCK, somatostatin, and Substance P) in order to assess the selectivity of the hormone expression.

NOMENCLATURE

Human preprogastrin comprises 101 amino acid residues (19). It consists of a signal peptide of 21 amino acid residues, a spacer sequence, the sequence containing the major bioactive forms of gastrin [i.e., gastrin-34 (pGlu 38–Phe 71), and gastrin-17 (pGlu 35–Phe 71)], and a COOH-terminal-flanking peptide (Fig. 1). In this study the following categories of preprogastrin products are distinguished: category I, amidated (bioactive) gastrins, in which the COOH-terminal phenylalanine (position 71) residue is amidated; category II, glycine-extended gastrins, defined as gastrin molecules processed to Trp–Met–Asp–Phe–Gly at the COOH terminus. These molecules are the immediate precursors of the bioactive gastrins; the glycine residue in position 72 being the amide donor (20); category III, progastrins, which are defined as products extended beyond glycine (position 72) at the COOH terminus; category IV, processing fragments, defined as products between monobasic and/or dibasic cleavage sites, devoid of the carboxyamidated COOH terminus. Fragments are denoted by numbers, indicating the position of the first and last amino acid. Each of categories I–III contains a number of peptides of different chain length, with or without sulfation of tyrosine-66.

MATERIALS AND METHODS

Tissue. Ovarian tumors were removed at surgery and immediately immersed in liquid nitrogen. Samples were stored at –80°C until extraction. Tumors were histologically verified and classified (21) as shown in Table 1. All patients were postmenopausal. Histologically verified nonneoplastic ovarian tissues were obtained from postmenopausal patients undergoing hysterectomy. The use of human tissues was approved by the local ethics committee.

Extraction. While frozen, tissues were minced and immersed directly in boiling water (pH 6.6), 6 ml/g tissue. The tissues were boiled for 20 min, after which tissues were homogenized and centrifuged at 10,000 × g for 30 min. After decantation of the supernatants, the pellets were reextracted in 0.5 M acetic acid for 20 min, homogenized, and centrifuged at 10,000 × g. Supernatants were stored at –20°C until assay.

Radioimmunoassays. In order to measure all biologically active forms of gastrin and CCK as well as their precursors, a library of sequence specific radioimmunoassays was used. The epitopes of the different antisera used in these radioimmunoassays are shown in Fig. 1. Bioactive (carboxy-amidated) gastrin and CCK peptides were measured using antiserum 2604, 2605, and 2609 which all are directed against the common α-carboxyamidated COOH terminus of gastrin and CCK. Antiserum 2604 binds all bioactive gastrins (sulfated as well as nonsulfated) with equimolar potency, whereas the cross-reactivity with CCK is negligible (22). Antiserum 2605 has characteristics identical to those of antiserum 2604, except that it measures only nonsulfated gastrins (22). Antiserum 2609 measures all biologically active forms of gastrin and CCK, sulfated as well as nonsulfated (22). Glycine-extended gastrin and CCK was measured using antiserum 3208, which is directed against the glycine-extended COOH-terminal sequences of gastrin and CCK (23). In addition antiserum 5284 was used. It binds only glycine-extended nonsulfated gastrins (23). Regarding progastrin, proCCK, and processing fragments, antiserum 2145 and 8017 are specific for the NH2-terminal sequence of human gastrin-34 (24) and the NH2-terminal sequence of human gastrin-17 (25), respectively. They bind

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The abbreviation used is: CCK, cholecystokinin.

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gastrin-34 and gastrin-17, as well as their COOH-terminally extended precursors. In order to measure NH2-terminal extended precursors as well, tissue extracts were incubated with equal volumes of trypsin (1 mg/ml in 0.05 M sodium phosphate, pH 7.5) at 20°C for 30 min. The enzymatic reaction was terminated by boiling for 30 min. By tryptic cleavage the NH2 termini of gastrin-34 and gastrin-17 will be exposed for binding to antisera 2145 and 8017, respectively. Consequently progastrin and its processing products are measured after tryptic cleavage (26). Another way of measuring COOH-terminally extended precursors is by using antisera 3208 and/or 5284 after sequential cleavage with trypsin (see above) and carboxypeptidase B (100 µg/ml sample). Both CCK and gastrin precursors are then bound to antisera 3208 and only unsulfated gastrins are bound to antisera 5284 (23). Recently, we developed a radioimmunoassay directed against the NH2 terminus of human gastrin-34 and gastrin-17, as well as against their amidation donor in the amidation reaction. Sul- 
fation can occur at the tyrosine residue in position 66. Gastrin-34 is constituted of amino acids Gln-38/ Phe-71 and gastrin-17 of amino acids Gln-55/Phe- 71. B. Localization of epitopes in the glycine ex- tended gastrins; C. localization of epitopes in the carboxyamidated gastrins. For antibody (Ab.) char-
acteristics see text.

Fig. 1. Structure of human preprogastrin. A. structure and mono- and dibasic processing sites of human preprogastrin. Numbers, characteristic amino acids. Serine 1 is the first amino acid of progastrin. The glycine residue at position 72 functions as amide donor in the amidation reaction. Sul- 
fation can occur at the tyrosine residue in position 66. Gastrin-34 is constituted of amino acids Gln-38/ Phe-71 and gastrin-17 of amino acids Gln-55/Phe- 71. B. Localization of epitopes in the glycine ex- tended gastrins; C. localization of epitopes in the carboxyamidated gastrins. For antibody (Ab.) char- 
acteristics see text.

Table 1 Concentrations of amidated gastrins and their precursors in extracts of ovarian tumors and in nonneoplastic ovarian tissue (pmol/g tissue, wet weight)

<table>
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<tr>
<th>Tumor</th>
<th>FIGO*</th>
<th>Amidated gastrins</th>
<th>Glycine- extended gastrins</th>
<th>Progastrins</th>
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<td></td>
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<td>0.5</td>
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<tr>
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<tr>
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<td>&lt;0.1</td>
<td>0.1</td>
<td>0.6</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>0.5</td>
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<tr>
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<td>&lt;0.1</td>
<td>0.2 ± 0.05</td>
<td>0.2 ± 0.06</td>
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</table>

*Classification according to International Federation of Gynecology and Obstetrics (FIGO) (21). Controls* mean ± SEM (n = 4).

RESULTS

As shown in Table 1, 12 tumors were classified as serous cystadenocarcinomas, 3 were classified as cystadenomas, 3 carcinomas were epithelial but nondifferentiated (tumors 13, 14, and 15), 1 tumor was mucinous (tumor 20), and 1 was a follicular cyst (tumor 21). The malignant tumors were in different stages of the disease [FIGO rating (21), Table 1]. In normal postmenopausal ovaria, amidated gastrins were undetectable (i.e., <0.1 pmol/g) and only low concentrations of glycine extended gastrins and progastrins were measured [0.2 ± 0.05 (SEM) pmol/g tissue and 0.2 ± 0.06 pmol/g, respectively (n = 4) (Table 1)]. One of the five benign ovarian tumors contained a little amidated gastrin (0.2 pmol/g tissue), while the concentrations of glycine-extended gastrins and progastrins were 0.1 ± 0.02 pmol/g and 0.5 ± 0.03 pmol/g (n = 5), respectively. In contrast, one-half of the malignant tumors expressed significant amounts of amidated gastrins [6.7 ± 2.7 pmol/g; range, 1.4–20.0 pmol/g (n = 7)]. The concentra-
tions of glycine-extended gastrins and progastrins were low (0.25 ± 0.03 and 1.4 ± 0.4 pmol/g, respectively) but higher than in controls and benign tumors (Table 1). The other half of the malignant tumors expressed glycine-extended gastrins and progastrins [0.2 ± 0.03 and 0.6 ± 0.1 pmol/g (n = 9)], but the amidation of the peptides was impaired (0.1 ± 0.03 pmol/g). One tumor [tumor 1, (Table 1)] con-
tained high amounts of progastrin fragment 38–54 (42.3 pmol/g before as well as after enzymatic treatment). In all other tumors the concentration of this progastrin fragment correlated to the concentration of other gastrin components (0.1–3.8 pmol/liter). In order to investigate if other NH2-terminal progastrin fragments than the 38–54 fragment were retained in Tumor 1, we measured the tumor extract with antisera 88235 before (14.7 pmol/g) and after (28.8 pmol/g) trypptic cleavage, while in all other tumors these concentrations varied between 0.7 and 4.6 pmol/g.

Gel chromatography of extracts of tumors 1 and 13 of Table 1, confirmed that the major part of the progastrin molecules were processed to amidated nonsulfated gastrin-17, eluting at $K_d$ 0.69. Low amounts of gastrin-34 ($K_d$ 0.48) and progastrin ($K_d$ 0.20) were also detected (Fig. 2; only results for tumor 1 shown; chromatography profiles of tumor 13 were identical).

To confirm that the majority of the gastrin-17 peptides was unmodified, tumor extracts were treated with trypsin prior to application on the column and fractions were measured using antisera 2604 and 2605, when the fractions were assayed with antisera 2604 (Fig. 3, left), a minor peak eluting at $K_d$ 0.56 (sulfated gastrin-17) and a major peak eluting at $K_d$ 0.69 (unsulfated gastrin-17) were detected. Measurement with antisera 2605 (Fig. 3, right), showed only the unsulfated component eluting at $K_d$ 0.69. The results shown for tumor 1 are representative for tumors expressing amidated gastrins at concentrations of 1.4 pmol/g and higher (tumors 1-4, 12–14), as judged by measurement using antisera 2604 and 2605.

The pattern of gastrin processing in tumor 1 was confirmed by gel chromatography using antisera 2145 and 88235 (Fig. 4). Tumor 1 contained high concentrations of progastrin fragment 38–54 (eluting at $K_d$ 0.58). The elution profile was identical before and after enzymatic treatment of the fractions, indicating a complete processing at dibasic cleavage sites Arg 36/Arg-37 and Lys-53/Lys-54. Measurement of the fractions with antisera 88235, revealed two components. The minor peak eluting at $K_d$ 0.69 corresponded to processing fragment 19–35 of progastrin as confirmed by calibration with synthetic progastrin 19–35. The major peak eluting at $K_d$ 0.53 was 3 times higher after enzymatic treatment of the fractions (Fig. 4) than before treatment (data not shown). Based on the facts that antisera 88235 reacts with reduced affinity with fragments unprocessed at Arg-19 and that the progastrin molecules in this tumor were fully processed at the dibasic cleavage site Arg-36/Arg-37 (Figs. 2 and 3), we assume that the immunoreactivity detected at $K_d$ 0.53 corresponded to progastrin 1–35 or 6–35.

Neither carboxyamidated CCK, glycine-extended CCK, proCCK, nor substance P were present in detectable amounts in the tumor extracts. Somatostatin and prosomatostatin were undetectable, except in tumor 20 which contained 1.5 pmol/g tissue (wet weight).

**DISCUSSION**

This study has shown that ovarian serous tumors express the gastrin gene. All tumors and normal postmenopausal ovaria expressed progastrin, the concentration of the total gastrin mRNA product being higher in neoplastic than in nonneoplastic tissue. The maturation of the peptides, however, differs between the tissues. The expression of gastrin is apparently selective, since other regulatory peptides such as CCK, somatostatin, and substance P are undetectable.

With the use of immunohistochemistry two studies (17, 18) found an increased incidence of argyrophilic cells containing gastrin immunoreactivity in mucinous ovarian tumors. This is in agreement with our observations in serous tumors. The immunohistochemistry studies used antisera, which bind both amidated gastrin and CCK. In view of our results, it is likely that the immunoreactivity is due to gastrin rather than CCK. Our study demonstrates gastrin in epithelial serous ovarian tumors [the most common type of ovarian tumor (28)] and normal ovaria. All previously published case reports (7–16) and the two histopathological studies (17, 18) described gastrin synthesis only in epithelial mucinous ovarian tumors. One case study found gastrin-34 to be predominant (7), in contrast to our findings in the serous tumors, where gastrin-17 is the most abundant gastrin peptide.

The detection of low amounts of progastrin and glycine-extended processing intermediates in the nonneoplastic ovaria indicates that the ovarian synthesis of gastrin is not ectopic. The total amounts of gastrin expressed by the malignant ovarian tumors were high compared to the control tissues, suggesting that the expression of the gastrin gene might be coupled to cellular events involved in the transformation of the ovarian epithelium. Transcriptional activation of the gastrin gene by epidermal growth factor and transforming growth factor α, which play a role in the promotion of ovarian carcinomas (29–32) and stimulate transcription of the gastrin gene (33, 34), might be responsible for the increased synthesis.

Malignant tumors containing 2 pmol/g or more gastrin were efficient in progastrin processing. In contrast, when the amount of total gastrin was below 1.7 pmol/g tissue, maturation of progastrin was poor in both malignant and benign tumors (Fig. 5). This observation cannot be accounted for by lack of sensitivity of the assays measuring amidated gastrins, since the detection limit of these assays is 0.1 pmol/g. The processing of progastrin in the malignant ovarian tumors is remarkable when compared to other major epithelial cancers expressing the gastrin gene (Fig. 6). The processing in the antral G-cells, the main site of gastrin synthesis, is efficient. The concentrations of progastrin and glycine extended gastrins are, consequently, low. The processing in the malignant ovarian tumors resembles that of the G-cells. In contrast, in bronchogenic carcinomas the processing is...
GASTRIN IN OVARIAN TUMORS

Fig. 3. Sulfation of amidated gastrins. Trypsin treated extract of tumor 1 was applied to the gel filtration column (for details see legend to Fig. 2) and measured with antiserum 2606 (left) and antiserum 2605 (right). s, sulfated; ns, nonsulfated.

Fig. 4. Gel chromatography of NH2-terminal gastrin processing fragments in extract of ovarian tumor I. Conditions were identical to those described in the legend to Fig. 2. Fractions were measured with antiserum 2145 before and after trypsin (•) (results were identical) and antiserum 88235 after tryptic cleavage of the fractions (□).

relatively poor and hypergastrinemia in lung cancer has not been reported (35). Colonic carcinomas do not process progastrin (36). Gastrin is also synthesized in acoustic neuromas (37). These tumors are rare and process progastrin poorly. Gastrinomas, also a rare type of tumor, express high concentrations of gastrin, but the processing of progastrin varies widely between the individual tumors (for review see Ref. 37).

Tumor 1 of Table 1 displayed an unique distribution pattern of gastrin processing fragments. The concentrations of NH2-terminal fragments 1–35 (or 6–35) and 38–54 of progastrin were unusually high in tumor 1 compared to the level of the other progastrin products detected in the tumor and compared to the other tumors (Figs. 2 and 4). The significance of this phenomenon is unclear. In tumor 1, a minor part of the progastrin was processed at the monobasic cleavage site at position Arg-19/Asp-20 of progastrin, as confirmed by gel chromatography. Recently, Huebner et al. (39) characterized the progastrin products in a pancreatic gastrinoma. Their tumor cleaved dibasic sites, but in addition it cleaved the monobasic Arg-5/Ser-6 site. The authors could not detect processing at Arg-19/Asp-20. In contrast, our data support the contention that Arg-19/Asp-20 is a processing site.

The nature of the gastrin synthesizing cells in the serous ovarian tumors is unknown, because the gastrin concentrations were too low to identify the cells by immunohistochemistry. In mucinous tumors, however, neuroendocrine cells have been described containing, among others, gastrin-like peptides and/or somatostatin (17, 18). In addition, in the mucinous ovarian tumors causing the Zollinger-Ellison syndrome, gastrin producing cells have been found scattered in the tumor. The patchy distribution of these cells may lead to variation in the measurements, especially since the majority of the tumors was large.

Fig. 5. Amidation ratio versus total gastrin content in malignant and benign ovarian tumors. Total gastrin content (pmol/g tissue, wet weight) of the malignant tumors (●) and benign tumors (△) of Table 1, plotted against the amidation ratio [amidated gastrin/total gastrin (%)].
Zollinger-Ellison syndromes caused by ovarian tumors are, as mentioned, rare. The total amount of gastrin synthesized by the ovarian tumors in this study is considerably lower than that synthesized at the main site of production, the antral G-cells. Consequently, it is difficult to assess the pathophysiological significance of ovarian gastrin expression. The cases reported thus far describe gastrin synthesis in three malignant mucinous tumors (8, 10, 16), in four mucinous tumors of borderline malignancy (7, 12, 13, 15) and in three benign mucinous tumors (9, 11, 14). Thus, in these cases amiation of gastrin was not correlated to malignancy of the tumor. No data have been given about the total amount of gastrin synthesis in relation to the degree of amiation. Gastrin production by ovarian tumors may cause, more commonly, moderate symptoms of gastrointestinal discomfort. Sporrorg et al. (17) reported the disappearance of gastrointestinal problems in one of the patients after surgical removal of a tumor of borderline malignancy that contained gastrin. The patients presenting with tumors 1 and 13 (Table 1) in our study had symptoms associated with hypergastrinemia. The patient with tumor 1 developed a duodenal ulcer 3 months before the ovarian tumor was diagnosed. Serum samples were unfortunately available only after operation. Metastasis of the tumor were present and the patient continued to have symptoms of hypergastrinemia. The concentration of amidated gastrins in serum after operation was elevated (119 pmol/liter; normal, <50 pmol/liter). The second patient was treated continuously for 5 years for duodenal ulcer disease prior to operation. The finding of gastrin in serous ovarian tumors suggests that female patients with persistent gastrointestinal disease and elevated serum gastrin concentrations may have ovarian cancer. Accordingly, measurement of gastrin in serum may facilitate early diagnosis of epithelial ovarian cancer, which is associated with a high lethality (40).

Since gastrin is known to be a trophic factor (2, 3, 41) local release of amidated gastrins may stimulate ovarian tumor growth by autocrine or paracrine mechanisms. Studies addressing such growth effects in ovarian cancer cells have now been initiated in our laboratory.

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