Gastrin in portal and peripheral venous blood after feeding in man

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SUMMARY The concentrations of immunoreactive gastrin in serum from portal and peripheral venous blood were determined in 10 patients with indwelling portal catheters before and after feeding. No significant differences were found between the gastrin concentrations in portal and peripheral serum. Gel filtration studies of serum did not reveal any differences between the gastrin components of portal and peripheral venous serum. Since neither the concentrations of immunoreactive gastrin nor the four gastrin components differed between portal and peripheral serum it is suggested that the liver is without effect on gastrin metabolism.

Portal caval shunting results in gastric hypersecretion of acid in the dog (Lebedinskaja, 1933; Clarke, McKissock, and Cruze, 1959), rat (Fisher and Snyder, 1965), and man (Orloff, Chandler, Alderman, Keiter, and Rosen, 1969). The mechanism is not yet elucidated. Available data indicate that the hypersecretion is mediated by humoral agents. These agents may either be derived from the gastrointestinal tract and escape inactivation by the liver due to the shunting or may be liberated from the liver after it has been deprived of its portal blood supply (Silen, Hein, Albo, and Harper, 1963).

Among other agents, gastrin has been implicated as the factor responsible for the hypersecretion following portal caval shunting (for references, see Thompson, 1969).

The purpose of the present study was to assess whether gastrin is affected by liver passage in man. The concentration and the distribution of components of immunoreactive gastrin in human subjects were measured directly by a radioimmunoassay technique.

Material and Methods

PATIENTS

Ten patients, four females and six males, age 51-71 years, were studied. All had primary malignant tumours in the lower gastrointestinal tract with suspected

metastases in the liver. Portal catheterization was performed in order to permit radiological studies of the hepatic portal system. In no patient was the presence of a liver metastasis detected.

TECHNIQUE FOR PORTAL CATHETERIZATION

The skin and linea alba was opened under local anaesthesia by a short midline incision between the umbilicus and the xiphisternum. The umbilical vein was identified, opened, and dilated with a bougie until the passage into the left branch of the portal vein was opened. A catheter (infant feeding tube no. 8) was then placed with its tip in the portal vein, secured in place, and the incision closed in layers. The position of the catheter was established by fluoroscopy (Dencker, Göthlin, Meeuwisse, and Tranberg, 1972).

DETERMINATION OF GASTRIC ACID OUTPUT

The patients were fasted overnight and a double-lumen gastric tube was introduced. The stomach was emptied, and basal gastric secretion was aspirated during one hour. Pentagastrin (Peptavlon) was given subcutaneously in a dose of 6 µg/kg and four further 15-minute samples were collected. The gastric acid output was determined by titration to pH 7. The results are given as basal acid output (BAO) and peak acid output (PAO, obtained by doubling the acid output during the 30 minutes of maximal secretion) expressed as milliequivalents per hour.

BLOOD SAMPLING

Collections were started at 9-10 hours am after fasting the patients overnight. Three blood samples were drawn from the portal and cubital veins at five-minute intervals, after which the patients were given a standard meal consisting of meat balls, potatoes, gravy, and a bottle of beer. After 15, 30, 45, 60, 90, 120, 150, and 180 minutes portal and peripheral samples were collected simultaneously. After separation the serum was lyophilized and kept at $+4^{\circ}\text{C}$ until gastrin analysis.

GEL FILTRATION OF SERUM

Serum samples, each of 1.5 ml, were applied to a Sephadex G-50 superfine column 10×2000 mm and eluted with 0.1 M sodium phosphate, pH 7.4, containing 0.6 mM ethyl-mercuric-thiosalicylate, at a constant flow rate of 5.4 ml per hour at 20°C . The column was calibrated with ^{125}I -albumin, mono-component porcine proinsulin, human insulin, synthetic human gastrin I, and $^{22}\text{NaCl}$. Each serum sample was mixed with ^{125}I -albumin monocomponent insulin and $^{22}\text{NaCl}$ before application to the column, for internal standardization. Fractions of 2.0 ml were collected, counted, and assayed for immunoreactive gastrin and insulin.

RADIOIMMUNOANALYSIS

Gastrin was measured by radioimmunoassay as previously described (Rehfeld, Stadil, and Rubin, 1972). Synthetic human gastrin was purified and monoiodinated by a modification (Stadil and Rehfeld, 1972) of the chloramine technique, resulting in a labelled gastrin with immunoreactivity indistinguishable from unlabelled synthetic gastrin. The detection limit of the assay was <0.2 pmol/l eluate, using the rabbit antiserum 2604-8 with a K° of 2×10^{12} l per mole. This antiserum was employed in a final dilution of 1: 180 000. The precision, specificity, and the accuracy of the assay has been evaluated in detail elsewhere (Stadil and Rehfeld, 1973). Immunoreactive insulin was measured by a wick-chromatographic assay with a detection limit of 5 pmol per l. Details on the parameters of the assay have previously been described (Rehfeld and Stadil, 1973a).

Results

Serum gastrin concentrations were abnormally high in the fasting state in three patients (fig 2). These patients had a low gastric acid secretion with a BAO of 0.06 ± 0.03 and a PAO of 4.0 ± 3.7 m-equiv/h (mean $\pm$ SEM). Acid secretory studies were obtained from three of the seven patients with normal serum gastrin levels; these had a normal acid output with

Fig 1 Immunoreactive gastrin concentrations in portal (closed circles) and peripheral (open circles) serum before and after feeding. Mean $\pm$ SEM, $n=7$.

Fig 2 Immunoreactive gastrin concentrations in portal (closed circles) and peripheral (open circles) serum in patients with hypergastrinaemia. Mean $\pm$ SEM, $n=3$.

Fig 3 Elution of immunoreactive gastrin (● - ●) in serum from two patients, A and B respectively, by gel filtration on Sephadex G-50 superfine columns, 10 × 2000 mm. The columns were calibrated with ^{125}I -albumin, proinsulin, insulin, and $^{22}\text{NaCl}$. Immunoreactive gastrin was distributed in four components, I-IV.

a BAO of 1.1 ± 0.7 and a PAO of 20.4 ± 7.8 mequiv/h.

Pre- and postprandial concentrations of gastrin in serum from portal and peripheral venous blood in the three hypergastrinaemic and seven normogastrinaemic patients are shown in figures 1 and 2. In neither group were there any differences between the fasting gastrin levels in portal and peripheral serum. Feeding induced a rapid increase in serum gastrin in both portal and peripheral blood with a maximum after 15 to 30 minutes, followed by a gradual decrease. In the hypergastrinaemic group there were no differences between the postprandial serum gastrin concentrations in portal and peripheral blood (fig 2). In the normogastrinaemic patients the serum gastrin levels after feeding were slightly higher in portal than in peripheral blood (fig 1). The differences, however, were small and

not statistically significant ($P > 0.05$, Student's *t* test for paired observations). The distribution of gastrin immunoreactivity in different gastrin components separated by gel filtration was found to be similar in portal and peripheral serum (fig 3).

Discussion

Portal-systemic shunting results in gastric acid hypersecretion, which seems to be due mainly to a marked augmentation of the intestinal phase of acid secretion (Clarke *et al*, 1959; Hayashi, Rheault, Semb, and Nyhus, 1968; Newman, Reeder, Davidson, Schneider, Miller, and Thompson, 1969; Thompson, 1969; Orloff *et al*, 1969). Spleno-caval shunting alone, in the dog, also produces hypersecretion, but of a lesser degree than mesenterico-caval shunting (Hayashi *et al*, 1968), indicating that

a gastric, humoral factor (gastrin) might also participate.

Studies on the effect of the liver on gastrin are somewhat contradictory. Several investigators have reported that gastrin is, at least partially, degraded or inactivated by the liver (Castaneda, Griffen, Nicoloff, Leonard, and Wangenstein, 1960; Kaulbersz and Bilski, 1962; Thompson, Reeder, Davidson, Charters, Brückner, Lemmi, and Miller, 1970; Beger, Kraas, Meves, Witte, Bittner, and von Hardenberg, 1972). On the other hand, Gillespie and Grossman (1962) did not find that portal administration of gastrin diminished the acid secretory response as compared to systemic administration, and McGuigan, Jaffe, and Newton (1969) found no differences in portal and systemic radioimmunoassayable endogenous gastrin in dogs. In experiments on dogs, Reeder, Brandt, Watson, Hjelmquist, and Thompson (1972) measured the total mass of endogenous gastrin entering and leaving the liver during basal conditions and after the stimulation of gastrin release by locally administered acetylcholine. They could not find any significant decrease in the amount of immunoassayable gastrin during passage through the liver. The results of the present investigation suggest that endogenous gastrin in man, as measured by radioimmunoassay, is not to any greater extent inactivated by the liver. The slightly lower gastrin levels noticed in peripheral blood are most likely caused by dilution only and are probably not to be considered a result of degradation or inactivation of endogenously released gastrin by the liver.

Even if the liver has little or no effect on synthetic, heptadecapeptide gastrin, it is evident, that penta-gastrin, which contains the biologically active C-terminal tetrapeptide of gastrin, is rapidly destroyed by the liver (Thompson *et al*, 1969; Temperley, Stagg, and Wyllie, 1971). This suggests that the liver might handle peptides with gastrin-like activity differently dependent upon their size. Gastrin in human serum is heterogenous. There appear to be at least four components of different molecular size (Rehfeld and Stadil, 1973b). By ion exchange chromatography it has been demonstrated that component I is unpaired, while components II-IV circulate as pairs. Each pair probably consists of one sulphated and one unsulphated isopeptide as is known for the heptadecapeptide gastrins (Rehfeld, Stadil, and Vikelsoe, 1973). The present study did not disclose any significant alterations in the pattern of gastrin components attributable to hepatic transit.

In conclusion, passage through the liver has not been found to affect the concentration or molecular size of immunoreactive gastrin in serum. These findings, however, do not disprove the hypothesis

that gastrin may be one factor responsible for the hypersecretion of acid after portal-caval shunting. The possibility still remains that the shunting procedure as such augments the release of gastrin from its cellular stores in the gastrointestinal mucosa.

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