Plasma Gastrin Responses to Arginine in Chronic Pancreatitis

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SUMMARY

Serum gastrin responses to intravenous L-arginine hydrochloride were measured in insulinopenic and noninsulinopenic patients with chronic pancreatitis and in suitable control subjects. There were no differences between any of the groups studied. Pancreatitis did not impair gastrin responses to arginine nor was gastrin an important determinant of insulin secretion in these patients. DIABETES *23*: **264-67, April, 1974.**

It has been previously demonstrated that patients with 'pancreatic diabetes' may have impaired insulin (IRI) responses to oral glucose[1] and intravenous tolbutamide[2] and depleted, but not absent, IRI reserve after intensive beta cell stimulation with combined glucose, glucagon and tolbutamide.[3] IRI release in response to intravenous arginine may also be impaired in patients with chronic pancreatitis.[4] In contrast, similar patients have been reported to have IRI responses to intravenous glucose comparable to responses of control subjects.[5] A lack of enhanced IRI responses to oral, compared with intravenous, glucose has been noted also in patients with cystic fibrosis of the pancreas.[6] These findings suggest the possible failure of a 'gut factor,'[7-13] exocrine pancreatic factors[5,14,15] or a pancreatic endocrine influence other than the beta cell[16] on IRI release in patients with pancreatic disease.

In a recent communication we demonstrated that intravenous arginine, a known IRI pancreatic glucagon and growth hormone secretogogue, was a potent stimulus for the release of gastrin.[17] Here we present data to show that gastrin responses to infused arginine are probably normal in patients with pancreatitis and the insulin insufficiency in some of these patients is unrelated to this 'gut factor.'

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PATIENTS AND METHODS

Eighteen patients with pancreatic disease were studied. The diagnosis of pancreatitis was suggested by abdominal pain associated with a raised serum or urinary amylase. The diagnosis was confirmed, in thirteen of fifteen patients tested, by abnormal secretin/pancreozymin pancreatic function tests;[18] laparotomy was performed in six cases, pancreatic pseudocysts developed in three and pancreatic calcification was demonstrated by radiologic studies in four. There were twelve males and six females; ages ranged from twenty-one to sixty-five years. Pancreatitis was associated with chronic alcoholism in fifteen patients and with cholelithiasis in one; in two cases no precipitating factor could be identified. None of the subjects had a family history of diabetes.

Seven healthy male volunteers, twenty-six to thirty-seven years old, constituted the control group.

After an overnight fast a polythene canula was inserted into a vein in the antecubital fossa. Basal samples were taken at -30, -15 and 0 minutes, and then 30 gm. L-arginine HCl in 150 ml. normal saline was infused over thirty minutes. Blood was taken at 5, 10, 20, 30, 35, 40, 50 and 60 minutes, mixed with heparin and Trasylol and centrifuged; the plasma was immediately deep frozen until assayed for gastrin. Immunoreactive insulin (IRI) was assayed in serum (taken at the same time) by the method of Hales and Randle[19] using Amersham kits. Gastrin was assayed according to the method of Hayes et al.[20]

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Total gastrin increments were measured by adding the increments at each time interval from five to thirty-five minutes. Total IRI increments were measured by adding the increments above fasting levels throughout the sixty minutes of the test.

Results were analyzed statistically using Student's *t* test.

RESULTS

Table 1 summarizes the hormonal responses to arginine in controls and patients.

IRI responses to arginine. The mean fasting insulin levels were similar in the control and patient groups. However, the total insulin increments in the patients varied considerably. Two groups were identified. Group I patients had total increments in the same range as the controls (39 to 337.5 μU./1 ml./1 hr.); the mean value for these patients was not significantly different from that of the controls, 101.3 ± 26.5 and 186.4 ± 69.2 μU./1 ml./1 hr., respectively. Group II patients secreted less insulin; the mean total insulin increment for this group was 16.4 ± 6.6 μU./1 ml./1 hr. ($p < 0.025$). Three patients in group I and five patients in group II had glucose tolerance test results indicative of diabetes.

Gastrin responses to arginine. The mean fasting gastrin level of the control subjects was 84.5 ± 17.1 μμg./1 ml. (range 20 to 200 μμg./1 ml.), which is similar to the mean level for all the patients (76.4 ± 15.3 μμg./ml.). Group II, insulinopenic patients, had a lower mean fasting level than group I, but the difference was not significant (see table 1). All control subjects and sixteen of the eighteen patients showed a significant rise in plasma gastrin levels in response to infused arginine (figure 1). The mean maximal increments for the controls and all the patients were similar (233.3 ± 45.1 and 228.9 ± 35.6 μμg./1 ml., respectively). The values for group I and group II patients were not significantly different. In twelve patients the gastrin rise was apparent within ten minutes after the arginine infusion was started; peak values occurred at any time during or five minutes after the end of the infusion. All responders showed a fall toward basal gastrin values within ten minutes after the infusion was completed (figure 1). Three patients, including two in group I and one in group II, failed to demonstrate a gastrin response to arginine. The mean total gastrin increments for the controls and all patients, and both patient subgroups, were similar. There was no correlation between the total gastrin and total insulin increments in any of the groups (table 1 and figure 2). An abnormal reaction to the glucose tolerance test did not influence gastrin secretion.

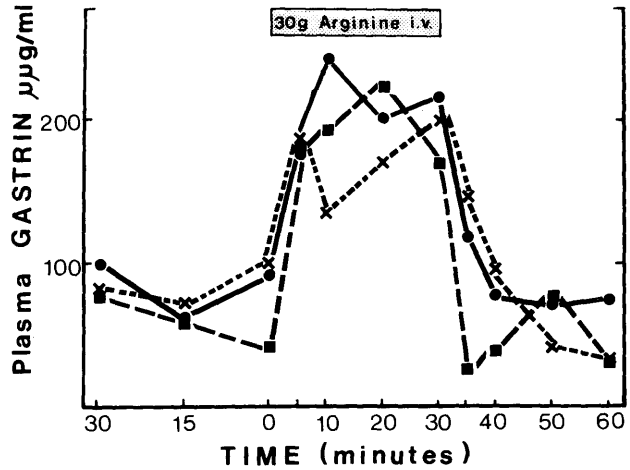

FIG. 1. Mean plasma gastrin responses to infusion of L-arginine monochloride in controls (●———●) and patients with chronic pancreatitis, including subjects with 'normal' insulin responses (x.....x) and insulinopenic patients (■----■). No significant differences occur at any time.

TABLE 1

IRI and gastrin responses to arginine

	Controls	Group I*	Group II
Fasting IRI (μU./ml.)	18.7 ± 3.5	15.7 ± 1.5	18.9 ± 2.7
Fasting gastrin (μμg./ml.)	84.5 ± 17.1	85.6 ± 24.2	61.9 ± 10.3
Total IRI increment (μU./ml./60 min.)	186.4 ± 69.2	101.3 ± 26.5	16.4 ± 6.6
Total gastrin increment (μμg./ml./35 min.)	561.8 ± 176.8	445.8 ± 133.2	460.3 ± 202.3
Maximal gastrin increment (μμg./ml.)	233 .3 ± 45.1	207.6 ± 42.5	258.8 ± 68.1

*Group I: Patients with 'normal' insulin responses. Group II: Insulinopenic patients.

There is no significant difference between fasting levels of IRI and gastrin in each group. Total IRI increments in controls and group I patients are not significantly different, but both are significantly greater than in group II patients ($p < 0.025$ and $p < 0.05$, respectively). There are no significant differences in total gastrin and maximal gastrin increments between any of the groups.

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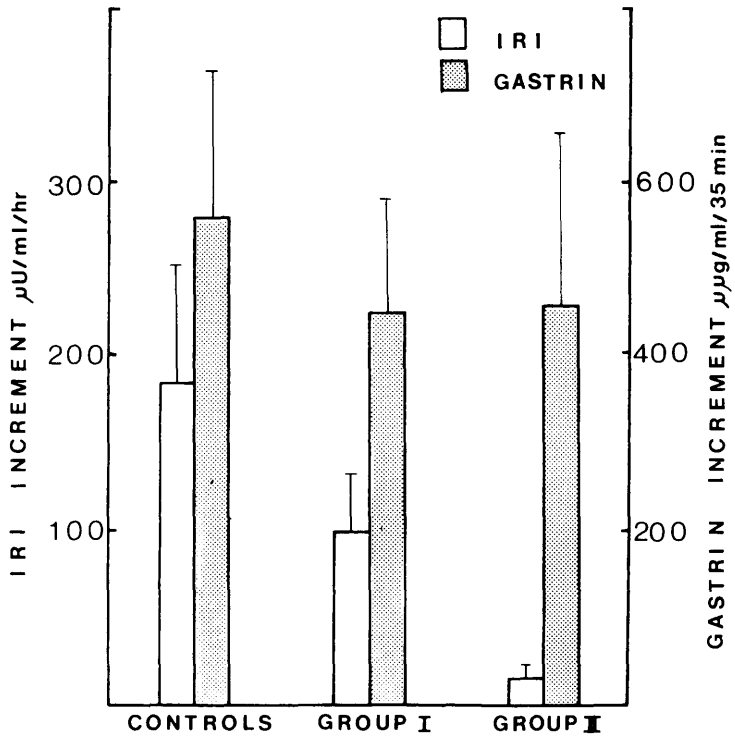

FIGURE 2

Comparison of the sum of mean increments above baseline for insulin and gastrin following L-arginine monochloride infusion in controls and patients with chronic pancreatitis, including subjects with 'normal' insulin responses (group I) and insulinopenic patients (group II). Gastrin responses remain normal, while insulin secretion progressively diminishes.

DISCUSSION

Fasting IRI levels and the IRI responses to the arginine infusion of the control subjects and group I patients are similar to those reported previously.[21-23] Although fasting IRI levels in group II patients were normal, their IRI responses to arginine were subnormal or absent. The low normal IRI output in most patients in group I and the subnormal response in all group II patients can be ascribed to islet damage associated with pancreatitis,[24,25] although there is some evidence that reduced IRI secretion in these patients may be related to diminished pancreatic exocrine function.[5,26]

The mean fasting gastrin level in the control subjects is higher than that reported by Korman et al.,[27,28] but similar to levels in the series of McGuigan and Trudeau.[29] Peak levels are also higher than those reported after protein ingestion.[27] It may be that high dose intravenous arginine is a more potent stimulus for gastrin release than a protein meal, but there may be differences in the gastrin assay systems used or the source of gastrin release.

The mean fasting gastrin levels in the patient groups were not significantly different from those in controls. The mean maximal gastrin increments for the patient groups were also little different from values in controls. Three patients showed no gastrin response to intravenous arginine, which may not be an invariable stimulator of gastrin release. In this regard McGuigan and Trudeau[29] reported absent gastrin responses to a protein meal, glycine, and bicarbonate ingestion in some healthy subjects; it is then quite likely that arginine will not invariably stimulate gastrin release. Nevertheless, the mean maximal and total gastrin increments of the patient groups and controls were not significantly different, suggesting that the gastrin secretion may have originated from gastric antral and duodenal mucosa[30] rather than from pancreatic 'G cells.' However, there is evidence that alpha cells are less damaged than beta cells in chronic pancreatitis,[4,31] and the same may apply to pancreatic 'G cells.'

Gastrin has been suggested as a possible hormone intermediary of the 'enteroinsular' axis,[13] but no quantitative difference was found in gastrin increments in controls or patients with normal or subnormal insulin responses. It can be concluded that gastrin deficiency does not play a significant role in reduced or absent insulin response in insulinopenic patients.

In conclusion it is apparent that intravenous arginine is a potent stimulus for gastrin release in the majority of subjects; most patients with chronic pancreatitis have a normal gastrin response to the infusion

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of this amino acid. The magnitude of the insulin response to arginine is not related to the magnitude of the gastrin response. Gastrin probably plays a minor physiologic role, if any, in insulin release from the pancreas.

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