Suppression and Stimulation Mechanisms Controlling Glucagon Secretion in a Case of Islet-Cell Tumor Producing Glucagon, Insulin, and Gastrin

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SUMMARY

The mechanisms controlling secretion of glucagon and other pancreatic hormones were studied in a patient affected with multihormone-secreting islet-cell tumor.

Fasting glucagon levels (3,000 pg./ml.) rose to 10 ng./ml. following arginine stimulation. While oral glucose load and intravenous glucose infusion did not suppress glucagon secretion, insuliin administration induced a prompt depression in glucagon levels. Glucagon, insulin, and gastrin levels were suppressed by somatostatin while calcium infusion caused a paradoxical increase.

It is suggested that only some of the stimulation-inhibition mechanisms were conserved in this case of glucagon-secreting pancreatic tumor. DIABETES *25*:408-12, May, 1976.

Following the first observation of McGavran et al.[1] of a glucagon-secreting-pancreatic tumor, others have reported islet-cell tumors producing glucagon alone[2-5] or in association with insulin and gastrin[6-8] or other extrapancreatic hormones (polyglandular adenoma syndrome).[7,9,10-12]

Glucagon-secreting pancreatic tumors are generally accompanied by a mild insulin-dependent[1-5] diabetes that, together with other, less frequent, clinical dermatologic symptoms, constitutes the main feature of the glucagonoma syndrome.

It is not known if the suppression-stimulation mechanisms controlling hormone secretion are conserved in glucagon-secreting tumors. Mortimer,[13] however, demonstrated that glucagon secretion was suppressed in a case of glucagonoma by hyperglycemia or infusion of somatostatin.

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Our recent observation of a case of multihormone-secreting (glucagon, insulin, gastrin) islet carcinoma presenting very elevated glucagon levels (3,000 pg./ml.) prompted us to study the homeostasis of the secretion of glucagon and other pancreatic hormones.

CASE REPORT

The patient was a 63-year-old woman. One of her brothers had undergone partial gastrectomy because of multiple ulcers. Beta-cell pancreatic-islet adenoma was diagnosed in one of her sons and subsequently removed.

Gastroduodenal ulcer was diagnosed in the patient when she was 45 years old. Gastroenteroanastomosis was performed and a partial gastrectomy was subsequently carried out because of anastomotic ulcer. Three years later, the patient underwent gastrectomy and a partial (body-tail) pancreatectomy because of islet-cell tumor. Microscopic examination carried out at that time revealed diffused adenomatosis, termed nesidioblastosis. The diagnosis of Zollinger-Ellinson syndrome was then proposed.

The patient was often subject to hypoglycemic crises during the next few years. When she was 59 years of age, hyperglycemia, accompanied by modest glycosuria and alternating with periods of normoglycemia, was observed. At 60, hepatomegaly was noted, which, within a few months, reached the transversal umbilical line. At that time the patient's weight fell to 35 kg. Upon admittance to our division, the patient was in a severe state of malnutrition and marked hepatomegaly. The patient also had stomatitis, raw tongue, and vaginitis.

Hepatic scintigraphy demonstrated an irregular ^{198}Au fixation. Laparoscopy revealed a pronounced hepatomegaly with a smooth surface dotted with white spots. Biopsy of one of these spots revealed an endocrine epithelial cell tissue with all of the characteristics of endocrine islet carcinoma. Elevated levels of pancreatic glucagon were present in an alcohol/acid extract of the metastatic tissue (1,250 pg./mg. tissue).

Endocrine-metabolic Studies

At admission, glucose fasting levels oscillated between 100 and 200 mg. per 100 ml., with glycosuria reaching 30 gm./day. No acetonuria was present. The patient was administered insulin (20-30 U./day) for 15 days, but treatment was suspended when hypoglycemic crises arose. At the end of this 15-day period, fasting glucose was 80-100 mg. per 100 ml. and glycosuria was less than 10 gm./day.

Fasting insulin levels at admission ranged between 100 and 200 μU./ml. (mean normal values in our laboratory = 16 ± 2 μU./ml.) and gastrin was 300-360 pg./ml. (normal values = 58±2 pg./ml.). Glucagon levels were approximately 3,000 pg./ml. (normal values = 105±15 pg./ml.) when determined with specific antiserum for pancreatoglucagon, K 30.

A slight hypercortisolism (20 μg./100 ml.) was present, while urinary steroids, plasma ACTH (which was determined by radioimmunologic method), and thyroid function were normal. HGH fasting levels were constantly high, ranging between 5 and 10 ng./ml. (mean normal values in our laboratory = 1.24±0.43 ng./ml.).

Calcium levels were constantly higher than 12 mg./100 ml. Both hypophosphoremia (from 1 to 2 mg./100 ml.) and hyperphosphaturia (>1 gm./day) were noted. Tubular reabsorption of phosphate was significantly reduced (about 60 per cent).

Ten days after the final phase of insulin therapy functional tests were carried out at 9 A.M. on different days following overnight fasting to determine the behavior of glucagon and other pancreatic hormones. The following tests were performed (figures 1 and 2):

(a) oral glucose load (100 gm.);
(b) L-arginine infusion (25 gm. in 30 minutes);
(c) intravenous glucose infusion (0.8 gm./min. for 90 minutes) with intermediate intravenous ad-

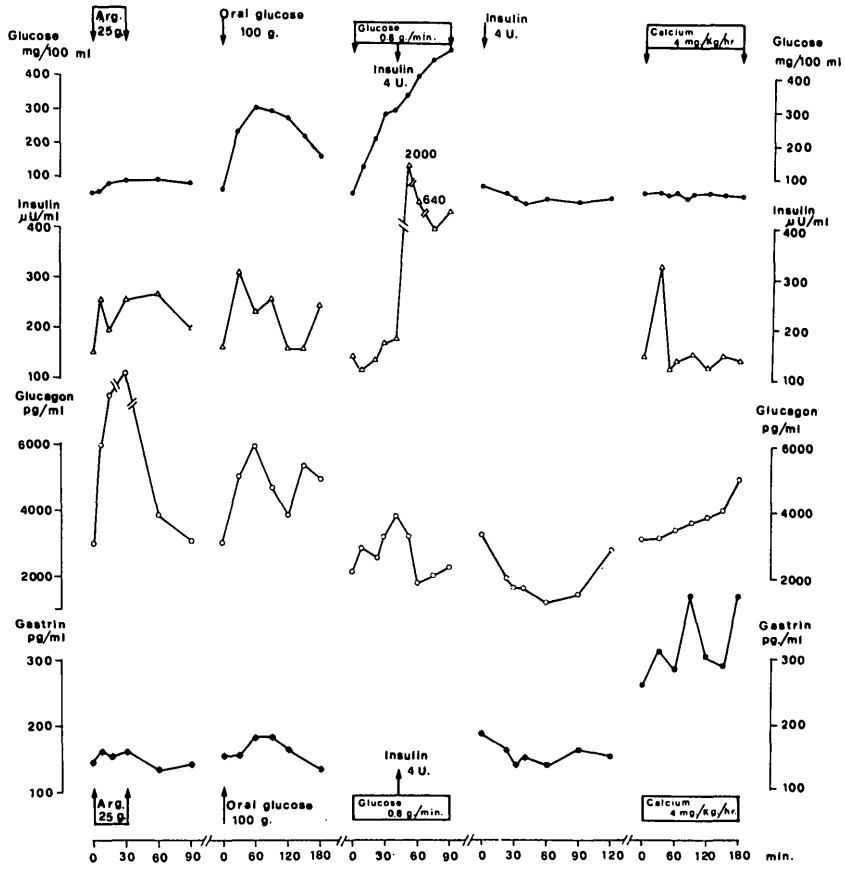

FIGURE 1

Plasma glucose, insulin, glucagon, and gastrin responses to arginine (25 gm. i.v. over 30 minutes), oral glucose (100 gm.), insulin administration (4 U.) carried out at 40 minutes of glucose infusion (0.8 gm. i.v./min. over 90 minutes), and alone, and calcium infusion (4 mg./kg./hr.) in a patient affected with islet-cell tumor.

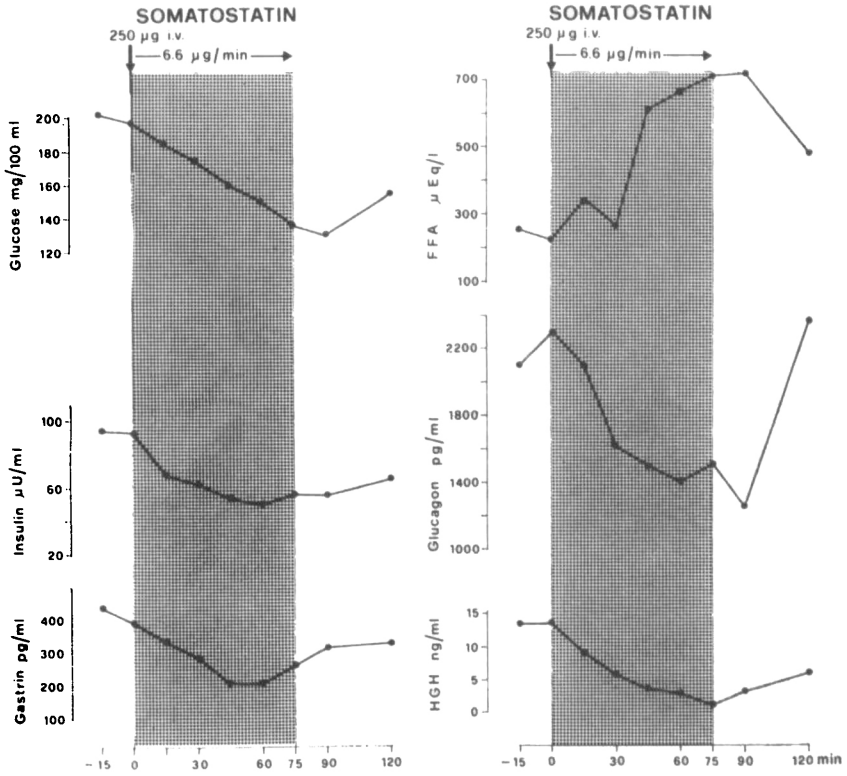

FIGURE 2

Effect of somatostatin bolus (250 μg.) injection (followed by 6.6 μg./min. infusion over 75 minutes) on plasma glucose, FFA, insulin, glucagon, gastrin, and HGH levels in a patient affected with islet-cell tumor.

ministration of insulin (4 U. at 40 minutes);

(d) insulin-test (intravenous administration of 0.1 U./kg. = 4 U.);

(e) intravenous calcium infusion (4 mg./kg./hr. for three hours);

(f) somatostatin infusion (GH-RIH bolus of 250 μg. followed by prolonged infusion of 500 μg. (6.6 μg./min. for 75 minutes);

(g) intravenous glucagon administration (1 mg.).

Plasma glucose (glucose-oxidase method),[14] FFA,[15] glucagon,[16] insulin,[17] gastrin,[18] and growth hormone[19] levels were determined. Specific antiserum for pancreatoglucagon, K 30, which was furnished by Dr. Unger (Dallas), was used for glucagon radioimmunoassay.

After glucose load an impaired glucose tolerance was observed. Insulin increased from 170 to 300 μU./ml. while glucagon levels reached 6,000 pg./ml. at 60 minutes. Gastrin levels were unchanged, while HGH increased, reaching 19 ng./min. at 90 minutes.

Arginine infusion induced slight variations in glycemia, a biphasic increase in insulin reaching peaks of 250 μU./ml. at five and 30 minutes, a marked increase in glucagon, which reached levels of 10,000 pg./ml. at 30 minutes, insignificant variations in gastrin values, and an increase in HGH, which reached 26 ng./ml. at 60 minutes.

Intravenous glucose infusion did not induce a significant increase in insulin levels, while glucagon was increased, reaching 4,000 pg./ml. *Rapid administration of insulin* at 40 minutes of glucose infusion induced a prompt depression in glucagon levels, which fell to less than 2,000 pg./ml. *Isolated insulin administration,* besides causing marked hypoglycemia, induced a prompt depression of glucagon levels, with a nadir at 60 minutes, corresponding to 1,020 pg./ml. This value had never been observed before in the patient. At 120 minutes, glucagon levels rose, reaching almost basal values.

Calcium infusion brought about a prompt stimulation of insulin secretion, which reached levels higher than 300 μU. after 30 minutes, and a slow but progressive increase in glucagon levels, which reached 5,000 pg./ml. A significant increase in gastrin levels, from 270 to 400 pg./ml., was observed during the test.

Infusion of somatostatin induced a progressive, prolonged reduction in glucose levels along with a depression in insulin (from 90 to 54 μU./ml.), glucagon (from 2,300 to 1,400 pg./ml.), gastrin (from 380 to 200 pg./ml.), and HGH (from 13.5 to 3.0 ng./ml.) levels. During infusion of GH-RIH, a progressive in-

crease in FFA was observed (figure 2). *Rapid intravenous injection of glucagon* induced a marked increase in glucose, a biphasic increase in insulin, with values higher than 300 μU./ml., and an insignificant increase in gastrin.

COMMENTS

The patient described can probably be classified as having a case of familial multiple endocrine adenomatosis, considering the presence of insulinoma in her son and of her own endocrine pancreatic islet-cell tumor associated with probable hyperparathyroidism.

The hyperfunction of the parathyroid could be attributed, according to Vance et al.,[7] to hypocalcemia induced directly by the hypersecretion of glucagon or to the release of calcitonin, which is also produced by glucagon.[20] It cannot be excluded, moreover, that the multihormone-secreting tumor itself produced ectopic parathormone. The increase in other extrapancreatic hormones, specifically in HGH levels, could be due to hyperinsulinism[7] and to the patient's periodic hypoglycemic crises.

The most important endocrinologic datum noted in the patient was a fasting hyperglucagonemia of approximately 3,000 pg./ml. This value is similar to those reported in the literature for glucagonoma where radioimmunologic dosage was specific for pancreatoglucagon (one case from Lightman and Bloom[4]—3,500 pg./ml.; three cases from Hayashi et al.[8]—960, 1,100, 1,300 pg./ml.; and four cases from Mallinson et al.[5]—1,500, 3,500, 1,475, 850 pg./ml.).

The study of glucagon-secretion regulation yielded some interesting results. While the suppression mechanism of somatostatin and the stimulation mechanism of arginine were conserved, a paradoxical glucagon response to hyperglycemia and hypercalcemia was observed.

Arginine stimulation demonstrated alpha-cell hyperresponsiveness by inducing a massive release of pancreatoglucagon, which rose from basal levels of 3,000 pg./ml. to 10,000 pg./ml. This observation is in direct contrast with those of Mallinson et al.[5] and Pek et al.,[21] who observed an absent or blunted glucagon response to arginine in patients with glucagonoma.

As regards the suppression mechanism of hyperglucagonemia, neither glucose per os nor intravenous glucose infusion induced a reduction in glucagonemia; instead, a paradoxical increase was observed. Pek[21] likewise reported no suppression of glucagon after oral or intravenous glucose administration. Vance et al.[7] observed hyperglucagonemia in a patient with multiple adenomatosis after oral glucose load or after tolbutamide, both of which should suppress glucagon secretion. However, Vance's assays were carried out with antiserum that was not specific for pancreatoglucagon. The lack of glucagon suppression by glucose could be due to the fact that glucagonoma produces not only true glucagon (3,500 MV) but, above all, proglucagon fraction (9,000 MV).[22] Glucose, in fact, suppresses only true glucagon fraction.

The lack of suppression of glucagon secretion by hyperglycemia is characteristic of the diabetic state.[23,24] In the diabetic situation, even if glucose is associated with the administration of insulin, a normal suppression of glucagon secretion is not obtained.[25] In our case, insulin administered during glucose infusion, and alone, induced a partial suppression of hyperglucagonemia. It was, however, necessary to bring plasma insulin levels to 2,000 μU./ml. before a significant glucagon suppression could be obtained. Evidently, the endogenous insulin levels (about 200 μU./ml.) were not sufficient to permit glucose to slow down alpha-cell production of glucagon. However, as observed in beta-cell adenoma, it is possible that the insulin determined by the radioimmunologic method is, in large part, proinsulin, which lacks the biologic properties of insulin.

In regard to the suppression of hyperglucagonemia by islet-cell tumor, Mortimer et al.[13] demonstrated glucagon suppression by a GH-RIH in the case described by Mallinson et al.[5] of glucagonoma. In our case as well, somatostatin induced a prompt, partial suppression of glucagon, insulin, and gastrin levels (figure 2).

While Unger did not observe any variation in glucagon levels during experimental hypercalcemia,[26] we observed an increase in glucagon secretion, especially at the end of the infusion. At the same time, insulin and gastrin secretion were highly stimulated. The increase in glucagon during calcium infusion is paradoxical, since it has been shown that deprivation of calcium causes an increase in glucagon secretion by isolated rat pancreas.[27] The increase of glucagon release during hypocalcemia rapidly declined in conditions of normocalcemia. On the other hand, excess of calcium had no effect on glucagon secretion.[27]

Finally, it should be pointed out that, despite chronic circulating hyperglucagonemia in our patient, the biologic, hyperglycemic, and insulinopoietic effects of exogenous glucagon persisted. In fact, in our

case, exogenous glucagon represented a very efficient insulinopoietic stimulus. These observations are in agreement with those of Yoshinaga et al.[2] and in contrast with those of McGavran et al.,[1] who observed in one patient that administration of 2.5 mg. of glucagon did not induce any increase in glucose or insulin levels.

From the results obtained in the study of this case of islet-cell tumor that produced glucagon, insulin, and gastrin, it is evident that the stimulation-suppression mechanisms of glucagon were only partially preserved. Despite hyperglucagonemia, the alpha cell responded markedly to arginine stimulus. Normal suppression mechanisms induced by glucose and calcium were absent. Partial suppression of hyperglucagonemia was observed only in the presence of elevated quantities of insulin. The suppressive effect of GH-RIH on glucagon levels was intact, thus confirming that the reduction of pancreatic hormone induced by somatostatin takes place through direct action of GH-RIH on the pancreas.

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