Islet Cell Tumors of the Pancreas: Clinico-Biochemical Correlations

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ABSTRACT

Islet cell tumors produce a spectrum of clinical syndromes. Intensive investigations of these tumors have enhanced our understanding of cellular origin, physiology and biochemistry of the islet hormones. Biochemical studies on the hormones are helpful in the diagnosis and treatment planning of the islet tumors. For example, insulinoma and glucagonoma can be diagnosed more readily by demonstration of proinsulin and proglucagon-like components, respectively, in the blood. Similarly, measurement of vasoactive intestinal polypeptide is not only useful in the diagnosis, but also in the follow-up of patients with pancreatic cholera syndrome. This mini-review examines these and other clinico-biochemical correlates seen in islet tumors.

The islet cell tumors are rare, with a prevalence rate of less than 1:100,000 population. However, these tumors have been the subject of great attention, since they pose a challenge to both basic scientists and clinicians. Investigations of these tumors have enhanced our understanding of embryogenesis of different cells of the islets of the Langerhans and about physiology and pathology of the hormones produced by the islet cells. The tumors produce a variety of clinical syndromes, the management of which is demanding to a clinician. In this paper, the biochemical and physiological actions of the islet hormones have been correlated with the corresponding clinical syndromes produced by the excessive hormonal secretions. This is not an extensive review of the subject, but it is aimed at developing the concept of clinico-biochemical correlations for islet cell tumors.

Embryology of the Islet Cells

The islet cells of Langerhans are probably a part of a system acronymed as "APUD," which stands for amine precursor uptake and decarboxylation. This system is derived from neurally programmed cells of the epiblastic origin. APUD cells are present in many organs and tumors, such as pituitary, thyroid, adrenal medulla, small cell lung car-

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cinoma, etc. These cells share many histochemical staining properties. Furthermore, support of their essentially neural nature is provided by the recent findings of at least two peptides common to brain and islets of Langerhans.

The Clinical Spectrum of the Islet Cell Tumors

Almost all of the benign and about three-fourths of the malignant islet cell tumors are recognized during life by the syndrome related to hypersecretion of one or more hormones. In table I are shown the cellular origin of various hormones of the islets, along with the syndrome produced by their excessive production. Many tumors may secrete more than one hormone. For example, several malignant insulinomas have been associated with secretion of multiple peptide hormones, including gastrin, glucagon, glucagon and gastrin, ACTH and serotonin. Occasionally, the tumor may occur as a part of the multiple endocrine adenomatosis (MEA-I) syndrome. The MEA-I syndrome is comprised of pituitary adenoma, islet cell adenoma, or carcinoma and parathyroid adenoma, or hyperplasia. About 20 percent of islet cell carcinomas do not secrete hormones, or at least not in high enough quantities that allow measurement with the present techniques, and present with abdominal mass, pain, jaundice or other symptoms. These tumors do not secrete human chorionic gonadotrophin (HCG) or one of its subunits (HCG-α or HCG-β).

Insulinomas

This is the most common islet cell tumor, although Zollinger-Ellison syndrome is also approaching the same prevalence rate in recent years. The peak occurrence of this syndrome is in the fourth to sixth decade. Anatomically, it may present as: (A) adenomas—single or multiple (are responsible for 80 percent of the insulinomas); (B) microadenomatosis; (C) carcinoma; (D) any of these associated with MEA-I syndrome; and (E) hyperplasia. Additionally, in children, nesidioblastosis, a condition characterized by genesis of beta cells and small islets from the pancreatic ductules, can cause intractable hypoglycemia.

The symptoms of insulinomas are usually related to hypoglycemia and can mimic a wide variety of psychiatric and neurological disorders. With the exception of carcinomas, which may present with a space-occupying lesion, all other anatomical forms of insulinomas present with hypoglycemic symptoms precipitated by periods of long fasting. Insulin produces hypoglycemia by interfering with a variety of mechanisms responsible for glucose homeostasis. Insulin interferes with processes involved in glucose production by decreasing inflow to the liver of substances needed for gluconeogenesis, as well as by decreasing the activities of the hepatic enzymes responsible for glucose production. Insulin also increases glucose and aminoacid intake and utilization in various tissues (see figure 1).

Diagnosis of Insulinomas

In a patient presenting with symptoms of fasting hypoglycemia, the diagnosis of insulinoma should be considered. In many patients, the plasma/glucose (G)
level after an overnight fast is usually below 60 mg per dl. However, in many patients, a prolonged fasting up to 14 hours is required to demonstrate a reduction of plasma glucose to below 50 mg per dl. A low plasma glucose, along with an elevated immunoreactive plasma insulin (IRI) is quite pathognomonic of insulinomas. A brief discussion pertaining to the role of insulin in glucose homeostasis is essential to appreciate the IRI/G ratio.

In normal individuals, secretion of insulin is determined by extracellular glucose. Most of the insulinomas are autonomic; therefore, a “normal” plasma insulin associated with fasting blood glucose in the hypoglycemic range is evidence that the secretion of insulin is inappropriate for the simultaneous blood glucose level. Others have suggested that an “amended IRI/G” calculated as: plasma IRI \( \mu U \) per ml × 100 divided by plasma glucose mg per dl minus 30 (with an upper limit of 50), would be a better ratio for the diagnosis. The subtraction of 30 mg per dl from the plasma glucose is based on the observation that at 30 mg per dl of plasma glucose, insulin secretion is almost totally switched off in healthy subjects.

There are a number of other provocative and suppressive tests which may be useful in the diagnosis of insulinomas. Assays of C-peptide and proinsulin are of considerable interest, since they demonstrate application of basic sciences to the clinical medicine. A brief discussion pertaining to the insulin synthesis and secretion will illustrate this point.

Many different proteins of diverging biological importance, such as hormones, antibodies, membrane proteins, are synthesized in the form of larger precursors that are subsequently modified by cleavage to smaller forms. Many recent studies have clearly demonstrated that initiation of protein synthesis occurs on polyribosomes in the cell matrix, and that the translation products of the m-RNA for various secretory proteins carry a 20 to 30 residue \( \mathrm{NH}_2 \) terminal extensions that contain a high proportion of hydrophobic amino acids. This hydrophobic \( \mathrm{NH}_2 \) terminal of proproinsulin serves as a leader at the ribosome membrane junction, leading to the vectorial discharge of the polypeptide in the rough endoplasmic reticulum (RER).

Immediately following the entry of the proproinsulin in the cisternae of the RER, the leader sequence is removed by specific peptidase, resulting in the formation of proinsulin. The prohormone then moves within the cisterne of the RER to the Golgi complex, where the aminoterminal peptide is further cleaved by trypsin and carboxypeptidase B, resulting in the production of insulin. The final hormonal product is packed into secretory granules and transported to the periphery of the cell. It is released into the extracellular space by the process of exocytosis, in response to an increased concentration of glucose in the extracellular fluid.

Normally, plasma proinsulin-like components (PLC) constitute less than 20 percent of the IRI. In almost all patients with insulinoma, plasma PLC contributes more than 25 percent of total IRI as measured by specific radioimmunoassay or by gel filtration. Although higher PLC activity is seen in other hypoglycemic states and rarely in other conditions, demonstration of this fraction in insulinoma patients is characteristic. More recently, gel filtration studies have demonstrated the presence of a high molecular weight IRI,
which could represent a counterpart of preproinsulin discovered in rat insulinoma.\textsuperscript{2,24} The inappropriate basal and stimulated release of insulin and proinsulin could be explained by a number of mechanisms. However, most of the evidence favors the hypothesis that in the insulinomas, there is a loss of storage capacity, combined with uncontrolled release of the hormones, owing to a defect in the intracellular insulin transport and release processes.\textsuperscript{6} The proinsulin molecule is composed of a C-peptide which links A and B chains of the insulin. The function of the C-peptide appears to be proper alignment of the chains, resulting in efficient formation of disulfide linkages.\textsuperscript{33}

When the proinsulin is converted to insulin by cleavage of C-peptide by trypsin carboxypeptidase B, the peptide is also released in circulation, and its release is proportional to endogenous insulin secretion.\textsuperscript{26} In normal volunteers, insulin infusion suppresses endogenous insulin secretion. Since most of the insulinomas are autonomous, there is an impairment of the feedback inhibition of endogenous insulin secretion.\textsuperscript{5} Service et al have used this principle in the diagnosis of insulinomas. They administered porcine insulin and measured C-peptide.\textsuperscript{31} During hypoglycemia (plasma glucose of less than 40 mg per dl), the mean C-peptide immunoreactivity (CPR) of normal subjects was less than 1.2 ng per ml, whereas with one exception, all patients with insulinoma had a mean CPR of more than 1.9 ng per ml.

**Glucagonomas**

Although glucagonomas were described many years ago, Mallinson and his coworkers described for the first time in detail the clinical glucagonoma syndrome.\textsuperscript{17} It is characterized by necrolytic migratory erythema, stomatitis, anemia, hypoaminoacidemia, mild diabetes mellitus, and weight loss. The single most characteristic feature seems to be the skin changes, and many of these patients may remain undiagnosed while attending dermatology clinics.\textsuperscript{36} The findings of hypoaminoacidemia and mild diabetes mellitus can be explained on the basis of increased glucagon levels, since the hormone is known to be antagonistic to insulin.\textsuperscript{36} The mechanism of dermatitis and anemia remains unknown. More recently, a patient was seen by us with glucagonoma who also manifested a diffuse neurological syndrome. Although the cerebral spinal fluid (CSF) glucagon in this patient was elevated, the exact mechanism of the neurological syndrome remains to be defined.\textsuperscript{12,24}

The diagnosis of glucagonoma is provided by immunocytochemistry and radioimmunoassay of glucagon.\textsuperscript{3,15,39} As with insulinomas, patients with glucagonomas also secrete high molecular weight precursor forms, and these can also be used for the diagnosis of the syndrome.\textsuperscript{3,39}

The glucagon measurements (IRG) may also serve in the follow-up of patients and to assess tumor response to various therapies.\textsuperscript{3} Our patient with glucagonoma received chemotherapy with multiple courses of 5-fluorouracil and streptozotocin, and plasma IRG was serially followed. The decline in the plasma IRG preceded his clinical improvement and has served as a useful marker for treatment planning.\textsuperscript{12,24} Serial follow-up with the markers, such as alpha fetoprotein or carcinoembryonic antigen, has been useful in the management of neoplasia and in other various tumors.\textsuperscript{18,20}

**Zollinger-Ellison (ZE) Syndrome**

The frequency of the ZE syndrome is fast approaching that of insulinoma. This syndrome results from the prolonged and excessive release of gastrin from a tumor also known as gastrinoma.\textsuperscript{30,38} Most of the clinical manifestations of the ZE syndrome are secondary to hypersecretions of gastric acid.\textsuperscript{30} Entry of large volumes of acid gastric juice is directly responsible for
duodenitis, duodenal and jejunal ulceration, and for the diarrhea frequently observed.\textsuperscript{25,38} Although volume and bicarbonate output of the pancreatic juice are also increased in gastrinomas, the capacity to secrete bicarbonate does not equal the capacity to secrete acid in these patients.\textsuperscript{38} This imbalance in acid bicarbonate secretion leads to low intraluminal pH, resulting in injury to the proximal intestinal mucosa. This impairs its ability to release normal amounts of secretin and to dissipate acid.

The diarrhea and steatorrhea associated with ZE are also secondary to excessive gastrin production.\textsuperscript{25} Gastrin inhibits salt and water absorption by the intestine. Similarly, large amounts of gastric contents (up to 10 liters per day) presented to the intestine and rapid intestinal transit times may also be involved in the pathogenesis of diarrhea.\textsuperscript{30} The low intestinal luminal pH caused by excessive gastric acid secretion, results in an activation of lipase and precipitation of bile salts. These factors, along with the damage to the intestinal mucosal cells, result in impaired ability to form chylomicrons, causing steatorrhea.\textsuperscript{38}

Tumors of the extra pancreatic endocrine glands are found in 20 to 48 percent of patients with the ZE syndrome.\textsuperscript{14} Although total gastrectomy has been the treatment of choice in managing patients with the ZE syndrome, recently cimetidine, an H\textsubscript{2}-receptor antagonist, has been found to be useful.\textsuperscript{19} These subjects are beyond the scope of the present review.

Somatostatinoma

Only three cases of somatostatinoma have been described.\textsuperscript{8,13,16} Two of these patients had a diabetic glucose tolerance curve,\textsuperscript{8,16} and in one case, steatorrhea and achlorohydria were also present.\textsuperscript{16} Two patients had exhaustive endocrine work-up. Excessive production of somatostatin in these patients was probably responsible for the marked suppression of basal and stimulated IRI, IRG and human growth hormone secretion.\textsuperscript{7,15,16} These cases have confirmed the physiological actions seen after the infusion of somatostatin in humans.\textsuperscript{26}

**Pancreatic Cholera (Werner-Morrison Syndrome)**

This syndrome, described first in 1958, is characterized by severe intractable, watery diarrhea, with hypokalemia, hypochlorohydria and occasionally hypoglycemia, hypercalcemia and episodes of flushing.\textsuperscript{27,28,37} The diarrhea is mostly of secretory type and results in the marked loss of water and electrolytes from the small and large intestines.\textsuperscript{28} The lesion most commonly underlying this syndrome is an islet cell adenoma or adenocarcinoma.\textsuperscript{27} A number of other tumors arising from “APUD” system may also cause this syndrome.\textsuperscript{15}

There is considerable evidence that the syndrome is caused by excessive secretion of vasoactive intestinal polypeptide (VIP).\textsuperscript{27,28} VIP in experimental animals causes induction of mucosal adenylate cyclase, which through cyclic AMP stimulates water and electrolyte secretion from the small and large intestines.\textsuperscript{23,28,32} There is also evidence that the VIP-cyclic AMP system may also be responsible for hypochlorohydria and hypoglycemia seen in this syndrome.\textsuperscript{32}

Some doubts have been expressed regarding the diagnostic value of plasma VIP measurements in the pancreatic cholera syndrome. Straus has pointed out the problems associated with the radioimmunoassay of VIP.\textsuperscript{34} It, therefore, seems that until more conclusive data are obtained, therapeutic decisions in cases of pancreatic cholera syndrome should be made more on clinical grounds than on the basis of VIP concentration. Moreover, cases have now been reported in which VIP levels were normal, whereas elevated
levels of prostaglandins of E series were found.\textsuperscript{11}

Conclusion

The islet cell tumors produce a spectrum of clinical disorders. Many of the symptoms and signs, characteristics of the specific islet cell tumors, can be explained by biochemical and physiological actions produced by the respective hormones of the tumors. In addition, many of the tests used in the diagnosis of these tumors are dependent on the biochemical actions of these hormones. A study of these tumors has led to a greater understanding of the biochemical and physiologic mechanisms of these hormones.

References

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