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PANCREATIC POLYPEPTIDE PPOMA

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ABSTRACT

Pancreatic polypeptide (PP) is a 36 amino acid peptide 93% of which is produced by F cells in the pancreas. PP has no real known actions (it stimulates pancreatic enzyme secretion and contracts the gallbladder) although earlier suggestions were that it might control appetite as a satiety hormone. However, PP levels respond dramatically to activation of the vagus by meals or hypoglycemia. Tumors of PP cells, PPomas, have been reported associated with watery diarrhea syndromes and mixed tumors may contain PP cells but multiple islet tumors are reported in MEN-1. There is speculation that many of the “non-secretory” tumors are in essence PPomas. Provocative tests include secretin stimulation and the sensitivity to vagal stimulation and suppression by atropine may distinguish normal from hyperplasia, nesideoblastosis and from tumors. These tumors are recognized by their highly vascular nature including the liver metastases. They do express somatostatin receptors and can be identified by somatostatin scintigraphy. Perhaps the most useful function of PP has been to identify autonomic neuropathy in which case the PP response to hypoglycemia is blunted. A new PP cell with neural connections has recently been identified and may impact future work on the neural connection of the pancreatic islet. Malignant PPomas are best treated with streptozotocin plus doxorubicin.

Pancreatic polypeptide (PP) was discovered by serendipity. In 1972, working in separate laboratories, Chance and Jones (2) and Kimmel and colleagues (3) independently purified a single major protein from a crude insulin preparation. The protein was named pancreatic polypeptide. In mammals, 93% of the cells producing PP are located in the pancreas. These pancreatic cells are known as F cells.

There are very dramatic effects on circulating levels of PP from meal ingestion, cerebral stimulation, and hormone administration. One study has shown an association between

increased PP levels and increased intraabominal fat, but not subcutaneous fat, as measured by CT scan (4). A clear cut biologic role for PP has not been established, however (5) (6) (7) (8). The only physiologic effects that are recognized in humans are the inhibition of gallbladder contraction and pancreatic enzyme secretion (8). Thus, a tumor deriving from PP cells is predicted to be clinically silent, although this is not always the case. Supraphysiologic levels of PP caused a sustained decrease in both appetite and food intake in normal healthy volunteers (9). A lower dose of PP (5 pmol/kg) showed similar effects in normal volunteers, suggesting PP is a satiety hormone (10).

Tomita and colleagues (11) reported two patients, one of whom had persistent watery diarrhea and the other high levels of circulating PP and PP-cell hyperplasia. A patient with chronic duodenal ulcer and a PP tumor also has been reported (12). A patient with MEN 1 syndrome presented with watery diarrhea, and it was found that only serum levels of pancreatic polypeptide were elevated (13) . A tumor that invaded the bile ducts, producing biliary obstruction, was a Ppoma (14). Pancreatic polypeptide cell hyperplasia found incidentally in a patient with intestinal obstruction has also been reported (15). It has been suggested that the watery diarrhea syndrome, which is seen in GEP endocrine tumors, may have its origin in PP overproduction (16). The picture is complicated by the fact that mixed tumors, PP-cell hyperplasia in association with other functioning islet cell tumors, ductal hyperplasia of PP cells, nesidioblastosis, and multiple islet tumors producing PP also have been described, either alone or as part of the MEN-1 syndrome (17) (18). Basal concentrations of PP in plasma may be raised above 1,000 pg/mL in 22 to 77% of all endocrine-secreting tumors and in 29 to 50% of patients with carcinoid syndrome, even if the carcinoid is located outside the pancreas. Among 53 patients with adenocarcinomas of the pancreas, however, no instance of an elevated basal concentration of PP was found (19) (20).

The diagnostic accuracy of elevated basal PP concentrations as a marker for endocrine-secreting tumors can be marginally increased to around 50 to 60% by determining the response of PP to secretin administration (21) (22). A response of greater than 5,000 pg/min/mL (i.e., integrated response) is more than two standard deviations above that observed in healthy subjects. It appears, however, that many cases of so-called nonfunctional GEP endocrine tumors are indeed PPomas, because 50 to 75% of these have raised basal PP levels and in 67% the response to secretin is exaggerated. Thus, in the absence of factors, such as chronic renal failure, that are known to cause marked elevation of PP levels, a markedly elevated PP level in an older, healthy patient occasionally may indicate a nonfunctioning pancreatic endocrine tumor. Differentiation of a high basal concentration in a healthy subject from that appearing in patients with tumor has been difficult(23) suggested that administration of atropine would suppress concentrations in healthy subjects and would fail to do so in patients with tumors, but this has not been subjected to extensive examination. (Assay available at Inter Science Institute-800-255-2873).

Increased PP cells are found in 20 to 67% of functioning and nonfunctioning tumors of the pancreas (24). There does not appear to be a relationship between the number of cells and their function because islet tumors containing subnormal, normal, or supernormal

concentrations of PP compared with that in the normal pancreas may be associated with normal or high levels of circulating PP.

There are now at least 25 patients in the literature with PPomas. Their age ranges from 20 to 74 years, with a mean of 51 years and an equal sex incidence. Diabetes was found in only two cases. Diarrhea, which formerly was thought to be a part of the syndrome (16), occurred in only one-third of cases. Steatorrhea was found in 100% of patients in whom it was sought. Decreased acid secretion was documented only in two of six people studied. Fifty-seven percent presented with weight loss. The PPoma syndrome is silent, and these tumors often are found unsuspectedly in the course of working up patients with hepatomegaly, abdominal pain, metastases to the liver, jaundice from obstruction of the common bile duct, or hematochezia.

Upper GI bleeding may occur because of invasion of the wall of the duodenum or thrombosis of the splenic or portal vein, with consequent development of varices. Not infrequently, PPomas are recognized by the radiologist as highly vascular tumors with metastases to the liver. Six of the reported cases had PPomas as part of the MEN-1 syndrome. A recent series of 4 patients with PPoma shows that these tumors can have a relatively benign clinical course. No recurrences were noted at a median of 49 months (25).

Some authors contend that not every patient with raised PP levels has a tumor (26) (21) (27) (24). Raised PP levels occur as part of the MEN-1 syndrome and may reflect nesidioblastosis of PP cells or multiple adenomata not amenable to resection.

It has been suggested that every patient with a markedly elevated level of PP should undergo exploratory laparotomy and careful inspection of the pancreas, even if the tumor cannot be diagnosed (11). This has not been our experience. If a tumor can be identified and localized, it should be removed. The frequency of malignancy of these tumors is not established, and resection should be reserved for those patients with clearly identified solitary lesions. Although rare, PPomas may occur in the chest and elsewhere outside the pancreas so laparotomy should not be performed routinely. Somatostatin receptor scintigrapy should be performed in such cases to localize the source of PP overproduction. If such a locus is found, the abdominal or other exploration should be performed. A complicating factor is pancreatic polypeptide cell hyperplasia can be SRS positive (28). Metastatic PPomas are best treated with streptozotocin plus doxorubicin. A new PP cell has been identified which has a neural innervation and may account for the responsiveness of PP to vagal stimuli. This may yet vindicate the belief of many that a role for PP is more than being a marker of vagal integrity!

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