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LEADING ARTICLE

Recent advances in pancreatic hormone research

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Introduction

The pancreas secretes 4 major polypeptide hormones: insulin from the beta cells; pancreatic glucagon from the alpha cells; somatostatin from the D cells in the islets of Langerhans, and pancreatic polypeptide (PP) from the PP cells which are spread more diffusely through pancreatic exocrine and endocrine tissue. Some or all of these 4 hormones may also have paracrine effects; this means that the peptide is secreted locally and has metabolic effects on neighbouring cells. Gastrin is synthesized in G cells in the foetal pancreas, but these cells disappear postnatally. Certain other polypeptides such as vasoactive intestinal polypeptide (VIP) have also been demonstrated in human pancreas, but appear predominantly localized to nerves; these substances, which were initially classified as 'gut hormones', are now thought to be neurotransmitters or neuromodulators of the non-adrenergic, non-cholinergic branch of the autonomic nervous system. In view of the multiple modes of actions of these peptides, the descriptive term 'regulatory peptides' is now often used. Basic information about the peptides to be discussed is listed in Table 1, but it should be emphasized that many of them exist in multiple molecular forms. The purpose of this review is to discuss some primarily non-diabetic aspects of the physiology and pathophysiology of pancreatic polypeptides which have recently received attention.

Physiology

The many metabolic functions of insulin are well known. Recently, much attention has been directed towards mechanisms of release. When equivalent amounts of glucose are given orally and intravenously, a much larger plasma insulin response is seen with the oral stimulus. It has therefore been postulated that there is a gut factor or 'incretin' which is released by the gut after glucose ingestion and causes the enhanced insulin secretion. The main candidate investigated has been gastric inhibitory polypeptide (also known as glucose-dependent insulinotropic polypeptide or GIP) which is a 43 amino acid polypeptide found in the K cells of the duodenum and jejunum. GIP is released after oral (but not intravenous) glucose and infusion studies have shown that, when the blood glucose level is raised above normal fasting levels, GIP releases insulin. It therefore appears that GIP is an incretin, but it probably does not explain the whole effect (Sarson and Bloom, 1981). This means that the search for other incretins continues and it seems likely that interest will now be turned towards the newly isolated glicentin.

The effects of glycogenolysis and gluconeogenesis of pancreatic glucagon and its release by hypoglycaemia and infusions of alanine and arginine are well known. It therefore antagonizes the action of insulin and, except in stress situations, its release is most inhibited by a high blood glucose. Some 30 years ago, gut glucagon-like immunoreactivity or enteroglucagon was recognized and it was subsequently shown that there were large amounts of this material in the L cells of the terminal ileum, colon and rectum. One such peptide, probably the most important, was glicentin (so named because it has *g*lucagon-*l*ike *i*mmunoreactivity) and appeared to be composed of about 100 amino acids. In 1981, Thim and Moody reported the 69 amino acid sequence of glicentin and demonstrated that in the 29 residues 33–61, there was the entire sequence of pancreatic glucagon. Pure glicentin is now becoming available (Moody *et al.*, 1981) and a study by Kirkegaard *et al.* (1982) in rats showed that glicentin inhibits pentagastrin-stimulated gastric acid secretion, but pancreatic glucagon does not. Another putative function for glicentin is as a trophic factor, particularly on small intestinal villous growth. Glicentin is released into the plasma in large amounts after a mixed meal and it seems likely that it will be found to have very different physiological effects from pancreatic glucagon.

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TABLE 1: Basic information on pancreatic regulatory peptides

	Molecular weight	Number of amino acids	Probable main mode of action	Main action
Insulin	5807	51	Hormone	Glucose lowering
Pancreatic glucagon	3485	29	Hormone	Glucose raising
Somatostatin	1640	14	Paracrine	Inhibition of hormone release
Pancreatic polypeptide	4226	36	Hormone	Inhibition of pancreaticobiliary secretions
Gastrin	2098	17	Hormone	Stimulation of gastric acid secretion
Vasoactive intestinal polypeptide	3326	28	Neurotransmitter	Noncholinergic, nonadrenergic, neurotransmitter

The biological effects of somatostatin are very great and it has been demonstrated to have a marked inhibitory effect on the secretion of most gastrointestinal hormones and fluid secretions (Table 2). Such widespread inhibition has led to the concept that it might be secreted by pancreatic D cells to have local paracrine effects on neighbouring cells, for example, the alpha and beta cells. Wass *et al.* (1980) have found considerable plasma somatostatin rises after a standard breakfast whereas we have only found rises after a very large meal. Our demonstration that exogenous somatostatin infusion during a small meal, to mimic plasma levels seen after a large meal, inhibits plasma hormone secretion suggests that somatostatin may act via the circulation and fulfil the criteria for being a hormone (Long *et al.*, 1982). Finally, as somatostatin has also been demonstrated by immunocytochemistry in autonomic nerves, it seems possible that it may act as a neurotransmitter or neuromodulator as well as a paracrine and hormonal substance. This peptide is therefore of particular interest as it may act through all 3 of the main modes of action attributed to pancreatic and gastrointestinal regulatory peptides.

TABLE 2. Effects of somatostatin

Inhibition of hormone secretion	
Site	Hormone
Pancreas	Insulin
	Pancreatic glucagon
	Pancreatic polypeptide
Stomach	Gastrin
Gut	Secretin
	Gastric inhibitory polypeptide
	Motilin
	Enteroglucagon
	Neurotensin
Anterior Pituitary	Growth hormone
	Thyroid stimulating hormone
	Adrenocorticotrophic hormone
Other	Calcitonin
	Renin
Inhibition of gastrointestinal secretion	
Gastric acid and pepsin	
Pancreatic juice	
Bile flow	
Small intestine	
Inhibition of other functions	
Splanchnic blood flow	
Gall bladder contraction	
LD^{50} of phenobarbitone	
Stimulation	
Gastric emptying of glucose	

Pancreatic polypeptide remains a hormone of uncertain function. In man, a large, rapid and persistent rise in plasma pancreatic polypeptide occurs after a mixed breakfast, but the best stimulus appears to be protein, for example, cod or beef. Pancreatic polypeptide is also released by insulin hypoglycaemia and gastric distension with either a balloon or non-nutritive substances. Normal secretion is almost entirely under parasympathetic control and can be inhibited by atropine or truncal vagotomy. In dogs, pancreatic polypeptide infusion causes inhibition of basal and secretin-stimulated pancreatic secretion (Lin *et al.*, 1976). Greenberg *et al.* (1978) infused bovine pancreatic polypeptide into normal human subjects to levels similar to those seen after a standard breakfast and found a significant reduction in biliary and pancreatic juice secretion along with reduced trypsin and bilirubin outputs. This experiment suggests that the persistent rise in plasma pancreatic polypeptide after a meal may be reducing late biliary and pancreatic secretion, but the physiological significance of the early rise remains obscure.

After birth, gastrin disappears from the pancreas, but this hormone keeps its interest as the great majority of gastrin-secreting tumours arise in the pancreas.

Vasoactive intestinal polypeptide (VIP) has been demonstrated in the pancreas in the exocrine parenchyma and around blood vessels, and VIP receptors have been demonstrated on pancreatic membranes. VIP stimulates pancreatic juice and bicarbonate secretion on a dose-dependent basis. When the vagus is stimulated, there is atropine-resistant, but somatostatin-sensitive, VIP release (Fahrenkrug *et al.*, 1979). These results suggest that VIP is acting as a neurotransmitter to control pancreatic exocrine secretion.

Deficiency syndromes

Chronic pancreatitis is a common cause of pancreatic endocrine dysfunction. The usual order of destruction of hormone cells is firstly pancreatic polypeptide, secondly insulin and thirdly pancreatic glucagon. The early loss of pancreatic polypeptide presumably reflects the presence of PP cells in the exocrine tissue as well as in the islets. In patients with chronic pancreatitis with steatorrhoea, the pancreatic polypeptide response to a mixed meal is highly significantly reduced compared to normal controls who have similar responses to patients with chronic pancreatitis and no steatorrhoea. The plasma pancreatic polypeptide response to intravenous Boot's secretin and to insulin hypoglycaemia is also usually reduced in patients with chronic pancreatitis with steatorrhoea. However, as occasional patients with chronic pancreatitis and steatorrhoea have normal pancreatic polypeptide responses, this test cannot be used for diagnostic purposes (Adrian *et al.*, 1979; Valenzuela, Taylor and Walsh, 1979). Insulin failure due to beta cell destruction may occur, as well as reduced pancreatic glucagon responses to stimuli such as intravenous arginine (Long, Adrian and Bloom, 1981a).

Children with cystic fibrosis have a poor mean plasma pancreatic polypeptide response to a milk drink. Interestingly, these children also have impaired glucose tolerance associated with a reduced plasma gastric inhibitory polypeptide response. This result suggests that there is a defect on the enteric side of the enteroinsular axis as well as an element of beta cell failure (Adrian *et al.*, 1980).

Pancreatic glucagon is thought to be essential for recovery from hypoglycaemia and it together with adrenaline are thought to be more important for this purpose than other counter-regulatory hormones such as growth hormone and cortisol. Recently, a diabetic patient was described who had recurrent severe hypoglycaemic episodes and, in response to insulin-induced hypoglycaemia, there was a poor response of plasma pancreatic glucagon, adrenaline, growth hormone and cortisol (Boden *et al.*, 1981).

Pancreatic glucagon and pancreatic polypeptide are both dependent on an intact vagus for their release. Krarup *et al.* (1979) showed a normal plasma pancreatic polypeptide response to insulin-induced hypoglycaemia in diabetes of short duration, but found that this deteriorated with time and that the deterioration correlated with parameters of peripheral neuropathy such as reduced vibration sense. They concluded that pancreatic polypeptide release might be used as a test for peripheral neuropathy in diabetics. Two other types of autonomic neuropathy have also been studied: in Chagas' disease, there is a destruction of post-ganglionic intrinsic cell bodies due to infection with *Trypanosoma cruzi,* and in chronic autonomic failure (the Shy-Drager syndrome), there is destruction of brain cell nuclei and intermediolateral spinal column cells. Both these groups of patients have a significant reduction of pancreatic polypeptide and pancreatic glucagon release to insulin-induced hypoglycaemia compared to controls (Long *et al.*, 1980; Barnes *et al.*, 1980). There is therefore a functional failure of pancreatic hormone release in each of the 3 types of autonomic neuropathy tested.

Bovine insulin treatment may be associated with large amounts of impurities which include other pancreatic peptides such as pancreatic polypeptide and VIP. In contrast, the newer porcine and human insulins are free from these contaminants. Many patients treated with bovine insulin preparations have been found to have developed antibodies to pancreatic polypeptide and VIP and, consequently, these peptides no longer circulate. The significance of this finding is unknown, but it has been postulated that the presence of VIP antibodies might encourage the development of autonomic neuropathy (Bloom *et al.*, 1979).

Nesidioblastosis is a rare disease of neonates characterized by prolonged periods of hypoglycaemia and the presence of circulating endogenous insulin which in normal people would be unmeasurable in the presence of a low blood glucose. In 1977, Hirsch *et al.* demonstrated that the hypoglycaemia could be reversed by small amounts of intravenous somatostatin. Subsequently, it has been shown that there are reduced amounts of pancreatic somatostatin cells in children with nesidioblastosis. It has therefore been concluded that this condition is due to pancreatic somatostatin deficiency.

Pancreatic endocrine tumours

Glucagonomas, PP-omas, somatostatinomas and vipomas became recognized in the 1970's and some of the basic background of these important, if rare, tumour syndromes is reviewed in Table 3. Pancreatic tumours secreting 5-hydroxytryptamine (serotonin), adrenocorticotrophic hormone and parathyroid hormone may also be seen (Friesen, 1982). It is

TABLE 3. Features of major pancreatic endocrine tumour syndromes

Tumour syndrome	Reference	Symptoms	Diagnostic features
Insulinoma	Friesen, 1982	Hypoglycaemia	Hypoglycaemia with hyperinsulinaemia
Glucagonoma	Mallinson *et al.*, 1974	Necrotizing, Migrating erythema; diabetes	Hyperglucagonaemia
PP-oma	Polak *et al.*, 1976	None recognized	Raised fasting plasma pancreatic polypeptide
Somatostatinoma	Krejs *et al.*, 1979	Diabetes; cholelithiasis; steatorrhoea	Raised plasma somatostatin
Gastrinoma	Friesen, 1982	Duodenal ulcers; malabsorption	Raised fasting gastrin with gastric hyperacidity
Vipoma	Long *et al.*, 1981b	Watery diarrhoea; weight loss	Raised plasma VIP; hypokalaemic acidosis

important to remember that these syndromes and their diagnosis can then usually be made by plasma radioimmunoassay of the suspected peptide. On occasions, supplementary investigations may be useful; these include the intravenous secretin test to demonstrate a paradoxical rise in plasma gastrin in gastrinoma patients, or the atropine test to demonstrate that pancreatic polypeptide is not under cholinergic control and therefore comes from a tumour. The anatomical site of the primary tumour can usually be demonstrated by selective pancreatic arteriography or portal venous sampling and subsequent radioimmunoassay of the tumour hormone to show a peak corresponding to the tumour venous outflow (Bloom and Long, 1982).

As discussed later in this issue, it is not uncommon for pancreatic endocrine tumours to produce multiple peptides (Dawson, Bloom and Cockel, 1983; Manche *et al.*, 1983). Combinations reported include gastrin and glucagon, insulin and gastrin, insulin and glucagon, gastrin and vasoactive intestinal polypeptide and pancreatic polypeptide with vasoactive intestinal polypeptide, glucagon, insulin and gastrin. Another feature is that the tumour may secrete multiple molecular forms of a peptide and, in one case, metoclopramide abolished diarrhoea in a vipoma patient by altering VIP secretion from the usual 28 amino acid form to a larger molecular weight form which appeared metabolically inactive (Long *et al.*, 1981c). The possibility of Wermer's syndrome (multiple endocrine adenomatosis, Type 1) must also be considered as sometimes pancreatic endocrine tumours, primary hyperparathyroidism and functioning pituitary tumours may all coexist simultaneously in a patient.

Surgical removal of pancreatic endocrine tumours is the treatment of choice, but is impractical in many patients because of large extensive primary tumours, multiple primary tumours or metastasis to liver and lymph nodes. H_2 receptor antagonists are gaining acceptance as a treatment for gastrinomas, but large doses causing an increased incidence of side effects may be required to control gastric acid secretion (McCarthy, 1980). The rash of glucagonomas may respond to zinc supplements. Vipoma diarrhoea has been reported to respond to a variety of treatments including indomethacin, metoclopramide, lithium, loperamide and trifluoperazine. Cytotoxic treatment with streptozotocin and 5-fluorouracil produces worthwhile remissions in many patients (Moertel, Hanley and Johnson, 1980). Arterial embolization of functioning tumour mass similarly may be dramatically helpful in some patients and is usually not associated with undue risk (Manche *et al.*, 1983).

Treatment with somatostatin

In view of its widespread biological effects (Table 2), somatostatin is of potential therapeutic use in many different clinical situations. Major problems of somatostatin as a treatment are its short plasma half-life (less than 5 min) and its broad spectrum of action. Subcutaneous protamine zinc somatostatin was found not to prolong, in a significant manner, the duration of action of somatostatin (Tannenbaum and Colle, 1980). At the Salk Institute, solid phase synthesis techniques have been used to develop peptides which have had aminoacids 1, 2, 4, 5, 12 and sometimes 13 deleted from the parent 14 amino acid somatostatin. These 2 somatostatin analogues have been found to be hydrophobic, to be released slowly from subcutaneous tissues into the plasma and to have a prolonged duration of action in animals and man when given subcutaneously. In contrast, the parent molecule is hydrophilic, rapidly absorbed and has a short duration of action; as a result, prolonged effects can only be produced by continuous intravenous (or possibly subcutaneous or intraperitoneal) infusion. Numerous attempts have also been made to synthesize analogues with specific actions, but analogues, which were shown to have insulin or glucagon specificity in rats, have been shown to have no such specificities in man (Adrian *et al.*, 1981).

A beneficial effect of somatostatin might be expected in diabetes mellitus as it delays intestinal glucose absorption, inhibits the secretion of counter-

regulatory hormones such as growth hormone and pancreatic glucagon and, in normal fasting subjects, lowers blood glucose concentrations. In insulin-dependent diabetics, insulin requirements were reduced by simultaneous insulin and somatostatin infusions (Gerich and Patton, 1978). However, when somatostatin and insulin were infused together in patients with established ketoacidosis, plasma glucose, pancreatic glucagon, free fatty acids and ketone-body levels fell as rapidly during insulin alone as during insulin and somatostatin infusion (Lundbaek *et al.*, 1976). In maturity onset diabetes, somatostatin worsens diabetic control by increasing plasma glucose, ketone and branched-chain amino acid concentrations (Tamborlane *et al.*, 1977). One clinical situation where continuous somatostatin infusion might be beneficial, is the rare acute diabetic retinopathy which is known to be growth hormone sensitive and to respond to hypophysectomy. It is possible that such patients might be spared the problems of hypophysectomy by this approach, but otherwise somatostatin treatment appears to have little to offer in patients with diabetes mellitus.

Treatment with somatostatin and its analogues has been studied in patients with various hormone-secreting tumours. In insulinoma, gastrinoma and glucagonoma patients, somatostatin reduces tumour peptide levels and in 2 patients improved the rash of the glucagonoma syndrome (Sohier *et al.*, 1980). Subcutaneous injections of 5 mg Des $AA^{1,2,4,5,12,13}$ somatostatin lowered tumour hormone levels below 50% of basal for 3–24 hr in 8 patients with pancreatic endocrine tumours (Long *et al.*, 1979), but subsequently it was shown that this analogue also inhibited the secretion of growth hormone and non-tumour-derived pancreatic and gastrointestinal hormones (Barnes *et al.*, 1981). In patients with the carcinoid syndrome, somatostatin abolishes spontaneous flushing and flushing due to alcohol, noradrenaline and pentagastrin; twice daily subcutaneous injections of Des $AA^{1,2,4,5,12}$ somatostatin greatly reduced flushing and lacrimation in a patient with severe carcinoid symptoms (Frolich *et al.*, 1978; Long *et al.*, 1981d). Somatostatin can also successfully control carcinoid diarrhoea (Dharmsathaphorn *et al.*, 1980). The long term use of somatostatin or its analogues is a potentially exciting new area of therapeutic advance in a variety of tumour syndromes.

Somatostatin has been used in the treatment of bleeding peptic ulcers on the basis that it both reduces gastric acid and pepsin secretion and splanchnic blood flow. In a randomized controlled study of patients with bleeding ulcers, somatostatin stopped the bleeding in 8 of 10 patients whereas cimetidine did in only 1 of 10 (Kayasseh *et al.*, 1980). In another study, somatostatin was effective in 17 of 23 patients who had previously failed to respond to cimetidine. Preliminary studies suggested that somatostatin might have a role in the treatment of bleeding gastro-oesophageal varices (Thulin *et al.*, 1979), but the effect of somatostatin on portal blood flow and wedged hepatic vein pressure in patients with cirrhosis is now controversial (Sonnenberg *et al.*, 1981; Bosch, Kravetz and Rodes, 1981) and a proper controlled trial is awaited.

The great potential for somatostatin therapy in many endocrine and gastrointestinal problems is obvious. Other potential uses include patients with acute pancreatitis (where a double-blind multicentre European trial should report soon and provide more definitive evidence) and to reduce leaking and hasten healing in postoperative abdominal fistulas (Gyr, Kayasseh and Keller, 1981). To date, almost no significant side effects have been encountered at standard dose rates, but careful metabolic studies are needed before more definite conclusions on long term safety can be reached.

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