Progress report

Hormonal control of pancreatic endocrine and exocrine secretion

The known inhibitory effect of glucagon on pancreatic exocrine secretion has recently been applied to the treatment of acute pancreatitis. The use of this promising therapeutic agent follows considerable advances made in recent years in the understanding of the hormonal control of pancreatic endocrine and exocrine secretion. Mechanisms of autonomic nervous control and of neuro-hormonal interactions in the pancreas have recently been reviewed by Brooks and Dupré.

Three questions about the hormonal control of pancreatic secretion need to be asked: How do pancreatic hormones (insulin and glucagon) affect exocrine pancreatic function (endocrine-exocrine interactions); how do hormones from the gastrointestinal mucosa affect endocrine function of the pancreas (entero-endocrine reactions); how do gastrointestinal hormones affect exocrine pancreatic function (entero-exocrine interactions)?

Endocrine-exocrine Interactions

There is evidence that the pancreatic hormones, insulin and glucagon, influence enzyme synthesis and release in the exocrine pancreas. Acinar cells in the rat pancreas show progressive degranulation and atrophy after repeated injections of glucagon. The inhibitory effect of glucagon on pancreatic exocrine secretion was first demonstrated by Zajtchuck and colleagues. Intravenous glucagon given to two subjects with pancreatic fistulae caused a 90% reduction in pancreatic juice volume and amylase. Dyck and his associates gave physiological doses of glucagon intravenously to the dog and man while stimulating pancreatic secretion with secretin and pancreozymin. Marked inhibition of enzyme output was noted and there was some reduction in volume flow while electrolyte concentrations were unchanged. The effect occurred within a few minutes, indicating inhibition of enzyme release rather than of synthesis. Knight and his coworkers treated three attacks of acute pancreatitis occurring in two patients with intravenous glucagon and the clinical condition of the patients improved rapidly. One patient received two intravenous injections of glucagon and the abdominal pain disappeared after four hours and the plasma amylase fell after seven hours. The second patient received a loading dose of glucagon followed by a glucagon infusion on two separate occasions. The pain was relieved and the plasma amylases fell after one hour. Although the trial was not controlled and the number of subjects small the results are promising and suggest that further use of the drug in the treatment of acute pancreatitis is indicated.

Progressive damage to pancreatic acinar cells is caused by insulin deficiency. The pancreatic exocrine tissue in diabetic man becomes fibroed and shows reduced response to hormonal stimulation and reduced pancreatic
uptake of selenomethionine$^{12,13}$, the changes being particularly marked in insulin-dependent diabetics. Dogs rendered diabetic with anterior pituitary extract$^{14}$ or alloxan$^{15}$ show damage to exocrine tissue, and alloxan given to rats results in a twenty-fold reduction in pancreatic amylase which returns to normal with insulin treatment$^{16}$. Insulin also increases synthesis of chymotrypsinogen in the pancreas of normal rats on an exclusively protein diet$^{18}$, and it was suggested that insulin controls the synthesis of chymotrypsinogen by favouring the entry of amino acids into the acinar cells and the synthesis of amylase by favouring the entry of glucose. Certainly insulin has been shown to promote amino acid incorporation and protein synthesis in isolated muscle$^{17}$ and secreting mammary gland$^{18}$. The role of insulin in protein synthesis has recently been reviewed by Wool$^{19}$ and Manchester$^{20}$.

There is some morphological evidence to indicate that pancreatic exocrine function may be influenced by pancreatic endocrine hormones. Henderson$^{21}$ has suggested that the endocrine tissue of the pancreas is fragmented into islets throughout the exocrine tissue thereby ensuring high concentrations of pancreatic hormones around the acinar cells which might have been of evolutionary advantage. In the human pancreas blood in the lobular arterioles first passes to the endocrine islet tissue and then forms a capillary plexus among the externally secreting acini$^{21,22}$. Henderson suggests that blood from the islets bathes the acinar cells by way of an islet-exocrine portal system. This relationship is found in reptiles, birds, and mammals. Primitive fish have a separate endocrine pancreas but cartilaginous fish show some endo-exocrine integration in having a double layer of cells lining the pancreatic ducts, a luminal layer of exocrine cells and an outer layer of endocrine cells. The fatty fibrosis of pancreatic exocrine tissue which follows diabetes mellitus is not reversed by therapeutic doses of insulin and Henderson argues that this is evidence in favour of acinar cell integrity depending on locally high concentrations of insulin delivered via the islet-exocrine portal system.

Hansson$^{23}$ has provided further evidence which may indicate pancreatic endocrine-exocrine interaction. Autoradiographs of mouse pancreas prepared after intravenous injection of $^{35}$S-methionine show that the amino acid is taken up markedly more strongly by the acinar cells surrounding the endocrine islets than by the cells remote from the islets. Kramer and Tan$^{24}$ have confirmed this observation and have shown that zymogen granules are more abundant in the perinsular acini but decrease to the levels of normal acini after islet destruction by alloxan. This suggests that insulin exerts a trophic effect on the perinsular acini by promoting amino acid uptake. Cells which have the ultrastructural features of both endocrine and exocrine cell types (intermediate cells) have recently been demonstrated$^{25}$. The fact that the intermediate cells occur mainly in the islets and periinsular acini and contain insulin and glucagon as well as secretory enzymes may indicate that the islet and periinsular acinar cells have a common origin and that functional endocrine-exocrine interactions are more complex than previously thought. The significance, in this context, of the hypothesis$^{26}$ that the islet cells and the polypeptide hormone-secreting cells of the gastrointestinal tract have a common origin from the neural crest of the embryo remains to be evaluated.

There is thus some phylogenetic, embryological, morphological, pathophysiological, and biochemical evidence of interaction between the endocrine and exocrine pancreas. The enhancement by insulin of amino acid uptake and synthesis would be highly relevant in the pancreas, for the pancreatic
acinar cells take up amino acids from the blood for enzyme synthesis more avidly than any other organ in the body.\textsuperscript{23,27} Promotion of amino acid uptake by insulin may explain why the uptake of amino acids is most pronounced in the acinar cells surrounding the islets and such an endocrine-exocrine interaction would fit Henderson's hypothesis. The role of the intermediate cells and the physiological significance of exocrine inhibition by pancreatic glucagon remain to be clarified.

**Entero-endocrine Interactions**

Pancreatic insulin and glucagon secretion is influenced by many hormones, including those released from the gastrointestinal tract. It is known that insulin\textsuperscript{28} and glucagon\textsuperscript{29} release from the pancreas is directly and reciprocally controlled by the blood glucose concentration. In addition insulin secretion is directly stimulated both by amino acids\textsuperscript{30} and fatty acids\textsuperscript{31} and glucagon is released by amino acids\textsuperscript{32}. Although the direct effects of nutrients on the endocrine pancreas appear to stimulate or inhibit release of insulin or glucagon appropriate to the physiological need it is becoming increasingly evident that hormonal control of insulin secretion plays an equal if not more important role. Glucagon is known to be a potent stimulus to insulin release\textsuperscript{33,34,35} and adrenaline is a powerful inhibitor\textsuperscript{36,37}. Insulin, in turn, affects glucagon secretion, for Unger and his associates\textsuperscript{38,39,40} have recently shown that normal suppression of glucagon secretion by hyperglycaemia does not occur when severe insulin deficiency is produced and this may explain the high levels of glucagon in the blood of subjects with diabetes mellitus. It is possible that these high levels of glucagon are partly responsible for the depressed exocrine function in this disease.

Glucose given by mouth is cleared more rapidly from the blood than glucose injected intravenously.\textsuperscript{41} McIntyre and his associates\textsuperscript{42} showed that delivery of glucose into the intestine in man is followed by higher blood levels of insulin than those reached when similar levels of blood glucose are produced by intravenous infusion. Since this enhancement of insulin release is not abolished by portacaval anastomosis\textsuperscript{43} it appears that the higher levels of insulin and enhanced glucose tolerance following absorption of glucose from the gut are due to an intestinal factor, possibly a hormone. The suggestion that there is a hormone in the gastrointestinal mucosa which stimulates insulin secretion is not a new one. Moore and his colleagues\textsuperscript{44} in 1906 suggested that the duodenum elaborates a hormone which excites the internal secretion of the pancreas. La Barre and his coworkers\textsuperscript{45,46,47} showed that the intravenous injection of a duodenojejunal extract into dogs causes hypoglycaemia and this effect is mediated by the pancreas. La Barre suggested the name 'incretin' for this intestinal factor which promotes glucose disposal. These early studies have been reviewed by Babkin\textsuperscript{48} and McIntyre\textsuperscript{49}.

Several of the hormones released from the intestinal mucosa are capable of stimulating insulin release but it is not yet known which hormone is the main stimulus to insulin secretion after glucose ingestion. The main candidates are secretin, pancreozymin-cholecystokinin, and enteroglucagon, a glucagon-like hormone found in the gastrointestinal mucosa. Blood concentration of a substance with glucagon-like immunoreactivity increases after absorption of glucose from the gut of man\textsuperscript{50,51} and dog\textsuperscript{52} but after intravenous glucose infusion immunoreactive glucagon levels fall\textsuperscript{51}. This suggests that
oral glucose stimulates release of immunoreactive glucagon from the gut but that intravenous glucose inhibits release of pancreatic glucagon by a direct effect on the pancreas. A substance with glucagon-like immunoreactivity has been found in the gastrointestinal mucosa and has been called 'gut glucagon' or 'enteroglucagon'. This substance has been shown to stimulate insulin release and could therefore be the intestinal factor which promotes glucose disposal during absorption from the gut. Cells containing a substance with glucagon-like immunoreactivity have been localized in the gastric fundus and jejunum of the dog using an immunofluorescent technique. Enteroglucagon can be distinguished from pancreatic glucagon by immunoassay and has twice the molecular weight and lacks the effects of pancreatic glucagon on liver glycogenolysis.

Other gastrointestinal hormones may also enhance glucose disposal in response to food in the gut lumen. Ingestion of glucose causes a rapid and large increase in circulating secretin-like activity and purified secretin given into the portal vein of the dog and man causes a significant rise in insulin release from the pancreas. The role of secretin in the normal physiological response to oral glucose has been cast in doubt by studies which fail to show a rise in plasma insulin after duodenal infusion of acid and no evidence of exocrine pancreatic stimulation (secretin effect) after intraduodenal glucose in man. More recently Chisholm and his associates have shown that an infusion of hydrochloric acid into the duodenum of man causes elevation of serum secretin and insulin levels. Further studies showed that the peak insulin response occurs 30 minutes after the peak secretin level and that the rise in blood insulin is greater and more prolonged than would be expected from the glycaemic stimulus alone or from the short-lived rise in blood secretin level. A continuous secretin infusion before the glucose ingestion was found greatly to potentiate the insulin response. This suggests that secretin has a dual role in insulin release, an early direct stimulation associated with raised secretin levels in the blood, followed by a prolonged potentiation of the glycaemic stimulus to insulin release which continues well after peripheral secretin levels have declined. It has also been shown by studies in vitro that secretin does not release insulin unless the exocrine pancreas is intact and this could be a further example of the mutual relationship mentioned earlier between the endocrine and exocrine pancreas.

Pancreozymin-cholecystokinin is the third intestinal hormone which may be responsible for the release of insulin after oral glucose, the stimulus to insulin release in this case being independent of the integrity of the exocrine pancreas. In addition, pancreozymin-cholecystokinin is the only gastrointestinal hormone that has been shown to stimulate glucagon release from the pancreas. As pancreatic glucagon is a potent stimulus to insulin release, pancreozymin-cholecystokinin could act as the stimulus for insulin secretion by a dual mechanism. It is possible that pancreatic glucagon released by pancreozymin-cholecystokinin partly counteracts insulin promotion of hepatic glycogen synthesis, allowing glucose to be acted on by insulin at peripheral sites.

Thus enteroglucagon, secretin, pancreozymin-cholecystokinin (and probably the chemically similar gastrin) may all fulfil the role of the hypothetical hormone, 'incretin', and act as signals for the release of insulin on the arrival of food in the gastrointestinal tract. Such an action would fill a physiological need.
Entero-exocrine Interactions

The actions of gastrin, secretin, and pancreozymin-cholecystokinin on the pancreas are well documented but incompletely understood. The mechanisms of release of these hormones have been reviewed recently by Wormsley70. It is known that these hormones have multiple and overlapping effects and the probability that gastrin serves as a direct stimulus to the release of secretin64 and secretin appears to inhibit gastrin release71 directly makes it likely that pancreatic exocrine secretion is serially controlled by more than one hormone. The synergistic actions between hormones72,73,74 and the difficulty of choosing physiological doses and administering them by way of the physiological portal venous route further complicates investigation. Chemical identification of the major gastrointestinal hormones has led to the development of radioimmunoassay of gastrin75, secretin68, and pancreozymin-cholecystokinin76, and this technique will be of undoubted value in our further understanding of the physiological roles of these hormones.

The possible role of enteroglucagon in stimulating insulin release has already been mentioned and it seems possible that enteroglucagon, like pancreatic glucagon, inhibits pancreatic exocrine secretion.

Dyck and his associates77 gave intrajejunal glucose to man while stimulating pancreatic secretion with secretin and pancreozymin. Bicarbonate concentration fell by 25% and volume by 50% and the fall was paralleled by a rise in blood levels of immunoreactive glucagon, presumed to be enteroglucagon. There was no change in enzyme concentration, contrasting with the marked fall in enzyme concentration after the intravenous infusion of pancreatic glucagon mentioned earlier8,9. It was postulated that pancreatic glucagon inhibits enzyme release while enteroglucagon inhibits volume flow and electrolyte secretion by the pancreas. The stimulus for this possible feedback mechanism would be the arrival of food in the intestine. The enteroglucagon released would regulate volume and electrolyte secretion while pancreozymin-cholecystokinin would, as mentioned earlier, stimulate release of pancreatic glucagon which in turn would regulate secretion of enzymes. However, the intrajejunal glucose used in this experiment was in 50% solution and the physiological relevance of the findings remains to be substantiated.

Grossman78 has postulated that gastrin, pancreozymin-cholecystokinin, secretin, and probably glucagon act on one receptor. The receptor has two interacting sites—one with affinity for the chemically similar gastrin and pancreozymin-cholecystokinin and one for secretin and probably the chemically similar glucagon. The hypothesis predicts that all targets that react to one of these hormones will react to the other two and probably glucagon as well. Simultaneous action of two hormones leads to competitive or non-competitive augmentation or inhibition, depending on whether the hormones are acting on the same or different interaction sites and whether the hormones acting on the receptor are stimulating or inhibitory. Glucagon appears to act on the receptor in a similar fashion. It shares with secretin choleretic79 and insulinotropic80,84,85 effects and the inhibitory influence on gastric acid secretion80 but the effects of glucagon on hepatic glycogenolysis and gluconeogenesis are not shared by the other gastrointestinal hormones81. Examples of all these forms of interaction have been found in the study of several of the target sites in the gastrointestinal tract. With the information
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provided by radioimmunoassay of levels of individual hormones, Grossman's hypothesis should enable a more detailed analysis of gastrointestinal hormonal action to be made.

Conclusion

The evidence reviewed demonstrates the complexity of the regulation of pancreatic exocrine and endocrine secretions and the difficulty of deciding which of the observed effects are of physiological importance. The hormones stimulating pancreatic exocrine and endocrine secretions interact by competing at the receptor site, by directly stimulating or inhibiting the release of other hormones, and, in the case of insulin, by controlling a-cell responsiveness to hyperglycaemia. It is suggested that hormonal control of insulin release is more important than the direct effect of blood glucose level and that the close anatomical relationship between the pancreatic islets and acinar cells enables locally high concentrations of insulin to promote uptake of amino acids by the acinar cells. The exocrine deficiency in diabetes mellitus may be due in part to lack of the trophic effect of insulin and in part to the raised blood glucagon levels found in this disease.

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