Nutrient Regulation of Insulin Secretion

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The role of the entero-insular axis in insulin secretion

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The concept of an entero-insular axis has its origins in the 19th Century, after the observation that greater amounts of glucose could be given orally rather than intravenously without producing glycosuria. However, convincing evidence that the gut is able to modify the insulin response to an oral glucose load was produced by two groups of investigators in the 1960s, who showed that oral glucose is much more effective in raising circulating insulin levels than intravenous glucose given in amounts sufficient to produce similar degrees of hyperglycaemia [1, 2]. The term 'entero-insular axis' embraces all those gut factors which contribute to enhanced insulin secretion after ingestion of a meal [3]. Gastrointestinal hormones, collectively termed 'incretins' [4], were regarded until recently as the major transmitters of messages from the gut to the pancreatic islets apart from absorbed substrates themselves and their metabolites. It is now apparent that the entero-insular axis possesses an important neural as well as an endocrine component. Both appear to work against the 'set' determined by the circulating insulin concentration. The endocrine arm of the entero-insular axis is better characterized, although far from completely understood. The following focuses on this arm, its role in the regulation of insulin secretion and the possible pathophysiological significance of its modification by dietary changes.

Investigators in the 1960s had assumed that higher circulating levels of insulin were synonymous with increased insulin secretion. This assumption has more recently been questioned as a result of comparing peripheral venous plasma insulin and C-peptide responses to oral and intravenous glucose. Observations [5] that the increased plasma insulin response to hyperglycaemia resulting from oral versus intravenous glucose was not accompanied by a comparable increase in plasma C-peptide, led to the conclusion that the higher plasma insulin levels seen after oral glucose were due to a decreased fractional hepatic extraction of insulin rather than increased insulin secretion. Further work, based on matching the degree of hyperglycaemia in arterialized rather than venous blood, which is more representative of the stimulus to insulin secretion at B-cell level, has shown that the incretin effect is mediated by both increased secretion and decreased clearance of insulin in normal human subjects [6]. Nevertheless, the observable effect of oral carbohydrate on peripheral insulin levels can be largely accounted for by augmented insulin secretion, particularly when large carbohydrate loads are taken orally [7].

Many peptides have been isolated from intestinal and nervous tissue which have the ability to stimulate insulin secretion. Notably, gastrointestinal peptides bearing a structural relationship to secretin all have the ability, to a greater or lesser extent, to stimulate insulin secretion [8]. The gastrointestinal hormone gastric inhibitory polypeptide or glucose-mediated insulinotropic polypeptide, better known by its acronym GIP, has, until recently, been thought to be the peptide with the most potent insulin-stimulating activity which is secreted in response to glucose [9]. Studies involving immunoneutralization of endogenous GIP in rodents suggest that GIP accounts for about 50% of the augmentation of insulin release seen after the administration of intraduodenal compared with intravenous glucose [10, 11]. Infusion of GIP antibody is more effective in abolishing the incretin effect in experimental animals that are unrestrained and unanaesthetized [12], possibly reflecting a difference in the contribution of the neural component of the entero-insular axis. Several other of the more recently isolated gastrointestinal peptides are secreted in response to oral, but not intravenous, glucose, including peptide histidine methionine and peptide YY, which qualifies them as potential mediators of the incretin effect [13]. In addition, a number of glucagon-like peptides are now recognized which have the ability to stimulate insulin secretion and which are secreted from the gut in response to oral glucose. They were initially characterized immunologically through their ability to cross-react with antisera raised against pancreatic glucagon and consequently designated glucagon-like immunoreactants (GLIs). Gradually a number of the GLls were characterized chemically, the best-known being glicentin, a 69-amino acid peptide of which the 33-61 sequence represents pancreatic glucagon [14], oxyntomodulin, a 37-amino acid peptide consisting of glucagon extended at the C-terminus by eight amino acids [15], and two glucagon-like peptides, GLP-1 and GLP-2, which have a high degree of sequence similarity with glucagon, suggesting that they were produced by triplication and subsequent sequence divergence of a single glucagon gene [16].

GLP-1 is located in both the pancreas and lower small intestine, with highest concentrations found in terminal ileum and colon [17]. In the pancreas it exists mainly as the 30-amino acid peptide, GLP-1 (7-36), from which the N-terminal hexaepitope of the larger form has been deleted [18]. This smaller form is a potent stimulator of insulin secretion in vitro [18, 19]. GLP-1 (7-36) has a potency equivalent to [18] or greater than [20] GIP in stimulating insulin on a molar basis from isolated perfused pancreas preparations. Recent infusion studies suggest that the insulin secretory potency of GLP-1 (7-36) is more powerful than GIP in molar terms in human volunteers, although its circulating level does not rise as high as GIP in response to an oral glucose load or test meal [21]. Even though the experimental data on GLP-1 (7-36) are still very scanty, present evidence suggests that it is likely to play an important role in the entero-insular axis, as the major incretin of the lower gut.

The influence of dietary composition on insulin secretion is well established. The mechanism by which diet modifies...
insulin secretion remains speculative, but some attention has focused on dietary manipulation of the entero-insular axis and in particular the dietary manipulation of GIP secretion. Glucose-induced increases in plasma GIP levels have been shown to increase both basal insulin and glucose-stimulated insulin secretion in experimental animals [22, 23] and in man an exaggerated GIP response to sucrose has been demonstrated in normal subjects after they have consumed a diet rich in sucrose for some time [24]. Changes in GIP secretion in response to changes in the fat content of the diet are particularly pronounced in rodents. A high-fat diet fed for only 4 days causes an increase in both GIP and insulin secretion in response to food, together with some degree of insulin resistance [25]. Rats fed a cafeteria-style high-fat diet exhibit exaggerated acute GIP and insulin responses to oral glucose when compared with animals fed on standard laboratory chow [26]. In man a similar, though less pronounced, effect is observed. An increased GIP response to oral glucose has been seen in human volunteers after a 35-day period of high-fat feeding [27]. This was not, however, accompanied by any changes in insulin secretion, even though glucose tolerance was improved by the diet, in contrast to what had been observed in similar studies in animals [25, 28]. Conversely, the GIP response to an oral fat load is attenuated in human subjects after consuming a low-fat diet for 35 days [29].

The demonstration that GIP secretion can be modified by dietary change suggests a mechanism whereby postprandial insulin secretion, its modification by dietary changes and its association with the pathology of various hyperinsulinaemic states may occur. Experiments involving dietary manipulation have shown that the hyperinsulinaemia characteristic of obesity may be partly a result of diet rather than exclusively a consequence of insulin antagonism [30]. Considerable evidence has accumulated linking diet and the entero-insular axis with the obesity–diabetes syndromes of hyperinsulinaemic rodents. In particular, the genetically obese hyperglycaemic ob/ob mouse exhibits marked hyperplasia of pancreatic islet cells [31] and exaggerated GIP responses to feeding glucose, amino acids or fatty acids [32, 33]. Despite the similarities between animal and human models of the obesity–diabetes syndrome, the role of the entero-insular axis in man is less well-defined. Conflicting results have been obtained of the GIP response to nutrient ingestion in diabetic patients with most recent studies indicating no abnormalities of GIP release or differences in the molecular forms of GIP secreted in response to nutrients [34]. There is similarly conflicting evidence as to whether GIP secretion is exaggerated in obesity [35–37]. These discrepancies may be due to differences in the habitual diets of the subjects, particularly the obese groups if they had been involved in attempts at weight reduction, a factor which has been ignored in the past.

GIP-induced insulin secretion forms just one part of the entero-insular axis. The modification of GIP secretion by dietary manipulation provides some explanation of observed dietary-induced changes in insulin secretion, but present knowledge is far from complete. Investigation of other incretins, notably GLP-1 (7–36), should prove rewarding in further elucidating the interrelationship between diet and insulin secretion.