NUTRIENT REGULATION OF THE ENTERO-INSULAR AXIS AND INSULIN SECRETION

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INTRODUCTION

Insulin plays a central and essential role in both carbohydrate and lipid metabolism. Elucidation of its mechanism of action and the pathological consequences of its deficiency in insulinoprivic (type I; insulin-dependent) diabetes (IDDM) has secured it a place in the textbooks of classical biochemistry. However, attention has been drawn, more recently, to other pathological consequences of insulin secretion which may be of particular relevance to our society. These include a spectrum of so-called 'Western Diseases', such as cardiovascular disease and type II or non-insulin-dependent diabetes (NIDDM), which have a strong dietary component in their aetiology and treatment. This review seeks to explore the mechanisms linking diet and insulin secretion in more detail, and to assess their relevance in the development and maintenance of diseases in which insulin action has been implicated.

The interrelationship between diet and insulin secretion is not novel; it is fundamental

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in the treatment of NIDDM, for example. Changes in the composition of the diet have been shown to affect circulating insulin levels in hyperinsulinaemic obese subjects (Grey & Kipnis, 1971) and, more recently in Australian aboriginals (O'Dea, 1984), both groups being at high risk of diabetes and cardiovascular disease.

A link between food intake and insulin secretion has, as its basis, the concept of an entero-insular axis. It was originally assumed that the major, if not only, stimulus to insulin secretion by the pancreas is the arterial blood glucose concentration. However, in 1964, two groups of investigators independently showed that oral glucose is much more effective in stimulating insulin secretion than intravenous glucose given in amounts sufficient to produce similar degrees of arterial hyperglycaemia (McIntyre *et al.* 1964; Elrick *et al.* 1964). McIntyre *et al.* (1964) postulated that nutrients taken by mouth stimulated the secretion of one or more gastrointestinal hormones, which in turn stimulated insulin, but did not exclude the possibility that other mechanisms might also be involved.

Potentiation of insulin secretion by gut factors is not confined to glucose-stimulated secretion. Dupre *et al.* (1969) demonstrated an augmented insulin response to an oral amino acid load compared to an intravenous one. The term 'entero-insular axis' was coined by Unger & Eisentraut (1969) to embrace all those gut factors which contribute to enhanced insulin secretion following ingestion of a meal. Gastrointestinal hormones were, until recently, regarded as the main, or possibly only, transmitters of messages from the gut to the pancreatic islets, apart from the 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 by modulating the pancreatic insulin response against the 'set' determined by the circulating blood glucose concentration.

Attempts have been made to quantify the relative contributions of the nervous system, hormonal factors and circulating levels of metabolites, to the insulin response to food. One study (Berthoud, 1984) estimated that neurally-mediated secretion accounted for 20%, and hormonal factors 30%, of the insulin response to a liquid test meal in rats. The contribution of the neural component of the entero-insular axis is a significant one, although comparatively little is known about it. Both the exocrine and endocrine components of the pancreas are subject to cholinergic, adrenergic and peptidergic innervation. Cholinergic innervation is responsible for enhancing the early insulin response to a meal, the so-called 'cephalic phase' of insulin release, which is independent of absorption of nutrients. Cholinergic mechanisms are also involved in the enhanced insulin secretion in obesity, the regulation of basal insulin secretion and post-prandial insulin secretion (Flatt & Bailey, 1984*b*; Ahren *et al.* 1986).

The pancreas is also innervated by peptidergic neurones, many of which contain 'gut peptides' that function as neurotransmitters. Vasoactive intestinal peptide (VIP) and cholecystokinin (CCK)-containing neurones have been implicated in the regulation of insulin secretion, but their precise role remains speculative. There is evidence that single neurones can contain more than one neurotransmitter and it is quite likely that their function is to modulate the action of the classical adrenergic and cholinergic neurotransmitters.

Although the endocrine component of the entero-insular axis is better characterized and more amenable to experimental manipulation via changes in nutrition than the neural component, it is still far from being completely understood. Nevertheless in the following discussion we will focus mainly on this arm of the entero-insular axis emphasizing its role in the regulation of insulin secretion and the possible pathophysiological significance of its modification by dietary changes. We also review mechanisms of insulin secretion in an attempt to interrelate the mechanisms of action of the gut hormones with absorbed substrates and their metabolites at the level of the pancreatic β-cell.

REGULATION OF INSULIN SECRETION BY NUTRIENTS AND THE ENTERO-INSULAR AXIS

GASTROINTESTINAL HORMONES AND INSULIN SECRETION

The modulation of glucose-mediated insulin secretion by gastrointestinal hormones is confined, in the main, to the endocrine arm of the entero-insular axis, although some gut peptides are located in the peptidergic neurones and may be activated by reflexes originating in the intestinal mucosa. Of the many peptides isolated from intestinal and nervous tissue some, notably growth-hormone-releasing factor (GHRF), vasoactive intestinal peptide (VIP) and gastrin-releasing peptide (GRP) share with gastric inhibitory polypeptide (GIP) a considerable structural similarity and an ability to stimulate insulin secretion (Dockray, 1987). The neuropeptide, galanin, likewise shares with neurotensin and somatostatin the ability to suppress insulin release under certain conditions. However whilst there is little evidence that either galanin or neurotensin plays a physiological role in the entero-insular axis, pancreatic somatostatin is now accepted as a paracrine regulator of insulin secretion. The endocrine role of somatostatin secreted by the antrum and small intestine in response to the ingestion of food is, however, less certain (Walsh, 1987).

Many gut hormones have the ability to stimulate insulin release. However, in order to qualify for a physiological role as endocrine mediators of insulin release they must not only stimulate insulin release at concentrations that occur in vivo but they must also be released in response to the ingestion of nutrients, especially glucose. The old-established, well-characterized gut hormones, secretin, gastrin, CCK and GIP all have the ability to stimulate insulin release under certain conditions. The insulin-stimulating effects of gastrin and secretin are, however, only weak, and effective only on glucose-stimulated insulin release (Lerner, 1977; Rehfeld & Stadil, 1983).

CCK was originally isolated from porcine intestine as a thirty-three amino acid peptide and this particular form of hormone is a relatively-weak stimulus to insulin secretion. Several smaller molecular forms have, however, now been isolated from gut mucosa as well as from the brain, where they may fulfill a satiety function, and both the carboxyl-terminal octapeptide (CCK-8) and tetrapeptide (CCK-4) have been found to be potent insulin stimulators in vitro (Okabayashi *et al.* 1983; Hermansen, 1984). There is, moreover, recent evidence, from human and animal studies, that physiological concentrations of CCK potentiate amino acid-induced insulin secretion (Rossetti *et al.* 1987; Rushakoff *et al.* 1987). Thus CCK may play an important physiological role in the entero-insular axis after the ingestion of proteins, but not of carbohydrates since these do not stimulate CCK release from the intestinal mucosa.

A number of glucagon-like peptides which have the ability to stimulate insulin secretion and which are secreted from the gut in response to the ingestion of glucose are now recognized, but their nomenclature is confused. They were initially characterized immunologically through their ability to cross-react with antisera raised against pancreatic glucagon (Samols *et al.* 1965). Consequently they were designated glucagon-like immunoreactants (GLI) or, less appropriately, enteroglucagon. Gradually a number of the GLI were characterized chemically, the best known being glicentin, a sixty-nine amino acid peptide of which the '33–61' sequence represents pancreatic glucagon (Thim & Moody, 1981), oxyntomodulin, a thirty-seven amino acid peptide consisting of glucagon extended at the carbon-terminus by eight amino acids (Bataille *et al.* 1982), and two glucagon-like peptides, GLP-1 and GLP-2, which have a high degree of homology with glucagon, suggesting that they were produced by triplication and subsequent sequence divergence of a single glucagon gene.

GLP-1 is located in both the pancreas and lower small intestine. In the pancreas it exists mainly in the thirty-six amino acid peptide form, and in the gut as a twenty-nine amino acid peptide (GLP-1_{7-36}) from which the nitrogen-terminal hexapeptide of the larger form has been deleted (Holst *et al.* 1987). This smaller form is the most-potent stimulator of insulin secretion of all the GLIs, and recent studies indicate that it is even more potent than GIP in molar terms (Kreymann *et al.* 1987), although its circulating level does not rise as high in response to an oral glucose load or test meal. Even though the experimental information on GLP-1 is still very scanty, present evidence suggests that it is likely to play an important role in the entero-insular axis.

Notwithstanding recent developments, GIP is generally considered to be the major endocrine component of the entero-insular axis (Creutzfeldt & Ebert, 1985). Although initially characterized in terms of its gastric acid inhibitory properties, GIP was subsequently shown to have a powerful insulinotropic effect, potentiating insulin secretion under physiological conditions in man (Dupré *et al.* 1973; Brown *et al.* 1975; Jones *et al.* 1987). GIP secretion from the K-cells is stimulated by contact with actively-absorbed carbohydrates (Sykes *et al.* 1980) but, on a molar basis, long-chain fatty acids are even more potent stimulants (Penman *et al.* 1981; Kwasowski *et al.* 1985).

GIP stimulates insulin secretion by the pancreatic β-cells only when blood glucose is raised above fasting levels; consequently GIP released from the gut when fat alone is ingested does not stimulate insulin secretion, thereby serving to safeguard against inappropriate insulin secretion and hypoglycaemia. When, on the other hand, a complex meal providing both carbohydrate and fat is eaten (as would naturally occur in a typical Western diet) circulating glucose levels rise and the GIP secreted in response to both its fat and carbohydrate components acts as a powerful stimulus to insulin release.

GIP secretion is seemingly dependent on the active absorption of nutrients rather than their mere presence in the gut lumen, thereby providing yet another mechanism for preventing inappropriate hyperinsulinaemia. The addition of phloridzin to an oral glucose load, for example, inhibits both the absorption of glucose and the release of GIP (Sykes *et al.* 1980), whilst patients with fat malabsorption caused by chronic pancreatitis show an impaired GIP response to oral fat which is partially restored by the addition of digestive pancreatic enzymes to the meal (Ebert & Creutzfeldt, 1980).

Negative feedback control by insulin on fat-stimulated GIP secretion can be demonstrated in man, and there is some evidence, from rat studies, that the C-peptide of proinsulin may also exert a similar inhibitory effect (Dryburgh *et al.* 1980). The negative feedback control by insulin is not seen with carbohydrate-induced GIP secretion (Andersen *et al.* 1978) serving, yet again, to distinguish between the two major classes of stimuli to GIP secretion.

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 (Ebert & Creutzfeldt, 1982; Ebert *et al.* 1983). The infusion of GIP antiserum was more effective in abolishing the incretin effect when the experimental animals were unrestrained and unanaesthetized (Lauritsen *et al.* 1981), possibly reflecting a difference in the contribution of the neural component of the entero-insular axis.

ACTION OF NUTRIENTS ON THE ENTERO-INSULAR AXIS

As explained previously, GIP is currently regarded as the major component of the entero insular axis. Consequently most studies into the effects of nutrients on the axis have focussed on GIP secretion, and these are reviewed in the following section. At the present time, there is little information available on nutrient interactions with the other potentially-

important insulin-stimulating gastrointestinal hormones, such as GLP-1 and CCK, and our understanding of the physiology of the entero-insular axis is correspondingly incomplete.

Amongst the nutrients, carbohydrate is undoubtedly the major stimulant of insulin secretion (Flatt & Bailey, 1984*a*). Different foods vary, however, in their insulin-stimulatory properties. Both chemical and physical forms of the carbohydrate are important. The so-called 'complex carbohydrates' are in general less hyperglycaemic and stimulatory of insulin secretion than their constituent monosaccharides (Crapo *et al.* 1976), Jenkins *et al.* (1981, 1984) have developed this observation under the concept of the glycaemic index, namely, the ability of carbohydrates to induce post-prandial hyperglycaemia relative to an equal amount of glucose. The physical form or texture of carbohydrate-containing foods also determines their ability to stimulate insulin secretion (O'Dea *et al.* 1980; Wong & O'Dea, 1983) as demonstrated by the effect of cooking (Collings *et al.* 1981), processing (Brand *et al.* 1985) and storing (Englyst & Cummings, 1987) on the glycaemic and insulin-stimulatory properties of various starch-containing foods. The cold-storage of potatoes, for example, markedly increases their amylase-resistant starch content with concomitant reduction in post-prandial insulin secretion (Englyst & Cummings, 1987). Carbohydrates are, however, almost invariably ingested as part of a mixed meal, and consequently the other nutrients present in the food influence the insulin-secretory response. The varying effects of different types of dietary fibre on oral glucose tolerance is now well established (Jenkins *et al.* 1978), as are the potentiating effects on the insulin response to glucose by the co-ingestion of fat. The complexity of the situation has recently been highlighted by Sud *et al.* (1988) in a study showing that the nutrient composition of a meal expressed entirely in chemical terms is a poor determinant of the insulinaemic and glycaemic responses to it, and the insulinaemic response to 'natural' foods, such as rice and green gram (*Phaseolus aureus* Roxb.), may be higher than to reconstituted foods equivalent in terms of their carbohydrate, fat, protein and dietary fibre content but differing in their physical and textural composition.

What are the mechanisms determining these differences in pancreatic endocrine response? The rate of hydrolysis of carbohydrates into their constituent monosaccharides, the place in the gastrointestinal tract where this takes place, and the rate of their absorption have all been implicated in the effect of physical form on insulin secretion (O'Dea *et al.* 1981). Moreover, the addition of certain types of dietary fibre to carbohydrate-rich meals can alter both the rate of gastric emptying and of glucose absorption with concomitant changes in insulin secretion (Jarjis *et al.* 1984). The question, therefore, arises as to whether changes in the contribution of the entero-insular axis are in any way responsible for the effects observed, especially since GIP in addition to its insulin-stimulatory effects may play the role of an enterogastrone, or inhibitor of gastric acid secretion and emptying (Brown, 1982).

GIP secretion in response to fat and carbohydrate ingestion is very selective and occurs mainly, if not exclusively, in the duodenum and jejunum. It is stimulated by carbohydrates only after their conversion into actively-absorbed sugars, such as glucose and galactose, and not at all by polysaccharides, disaccharides, passively-absorbed sugars such as fructose, or polyol sweeteners such as xylitol (Sykes *et al.* 1980; Salminen *et al.* 1982). Fat-induced GIP secretion is stimulated by long-chain fatty acids and triglycerides but not by short-or medium-chain fatty acids (Kwasowski *et al.* 1985). The effect of non-absorbable fats such as sucrose polyesters, e.g. olestra, is unknown at the present time. Differences in GIP secretion could, therefore, theoretically account for some of the observed variations in insulin secretion when carbohydrates of differing chemical composition are ingested.

It seems likely that GIP secretion is directly related to the rate as well as to the site of absorption of nutrients. Addition of the soluble fibre guar gum to a carbohydrate meal slows down the rate of absorption of glucose across the small intestine (Blackburn *et al.*

1984) and reduces the blood glucose, insulin and GIP responses to the meal (Morgan *et al.* 1978, 1985). The close correlation observed between post-prandial GIP and insulin levels in guar-gum-supplemented meals suggests that changes in the entero-insular axis are in part responsible for effects of guar gum on insulin secretion.

However, when fat is added to a carbohydrate meal it lowers only the post-prandial blood glucose response, leaving the insulin response either unchanged or increased (Collier, 1984). Co-ingestion of fat with a carbohydrate meal increases the GIP response beyond that produced by the carbohydrate alone and provides the most-likely mechanism for the observed potentiation of the insulinaemic response observed under these circumstances.

These examples suggest that insulin secretion is closely linked to that of at least one of the major gut hormones and provide a mechanism whereby long-term changes in diet might modify the acute insulin response to nutrient stimuli in the absence of overt metabolic dysfunction.

DIETARY MANIPULATION OF THE ENTERO-INSULAR AXIS

The literature concerning the effect of dietary composition on insulin secretion in animals and man is extensive and often contradictory. It has, for example, long been recognized, as a result of experiments involving dietary manipulation, that the hyperinsulinaemia characteristic of obesity may be partly a result of diet rather than exclusively a consequence of insulin antagonism (Grey & Kipnis, 1971). However, the mechanisms by which diet influences insulin hypersecretion remain speculative.

Diets high in sucrose have been shown to increase basal insulin levels and glucose-stimulated insulin release in experimental animals (Hallfrisch *et al.* 1979; Kergoat *et al.* 1987) and in man an exaggerated GIP response to sucrose has been demonstrated in normal subjects after they have consumed a diet enriched with sucrose for some time (O'Dorisio & Cataland, 1981). A direct relationship may, therefore, exist between the exaggerated GIP response and increased plasma insulin levels observed in experimental subjects on high-sucrose diets, possibly due to enzyme induction leading to more-rapid hydrolysis of sucrose into its constituent monosaccharides.

The concept of a metabolic interaction between the two peptide hormones, insulin and GIP, in response to dietary manipulation is strengthened by the observation that high-sucrose diets enhance insulin action in adipocytes from experimental animals (Kergoat *et al.* 1987) and that GIP activates liprotein lipase and consequently hastens chylomicron clearance from the circulation by adipocytes (Eckel *et al.* 1978; Wasada *et al.* 1981).

However, changes in the hormones of the entero-insular axis in response to changes in the fat content of the diet are more pronounced than to changes in the amount of carbohydrate in animal studies. Rats, fed on either a cafeteria-style high-fat diet or a glucose-supplemented diet, for example, exhibit exaggerated acute plasma GIP and insulin responses to oral glucose when compared with animals fed on standard laboratory chow, but the effect is most marked in the cafeteria-fed group (Tan *et al.* 1987). Rats are seemingly very sensitive to changes in the fat content of their diet. A high-fat diet, fed for only 4 d causes both an increase in GIP and insulin secretion in response to food and some degree of insulin resistance (Hampton *et al.* 1983). Fat-fed rats also lose negative feedback control by insulin of fat-stimulated GIP secretion, thus an overactive entero-insular axis could be implicated, at least in part, in the pathological development of hyperinsulinaemia such as that observed in asymptomatic subjects with covert atherosclerosis.

A normal rodent laboratory diet provides less than 10% of its energy as fat. This compares with a 40% provision by fat in the typical human Western-type diet. Caution must, therefore, be exercised when extrapolating the relevance of rodent experiments to man. Nevertheless the feeding, short-term (11 d), of a high-fat diet to human volunteers had a

similar, though less-pronounced, effect to that observed experimentally in rats. Human subjects exhibited resistance to the hypoglycaemic action of exogenous insulin after short-term high-fat feeding and lost feedback control by insulin on fat-stimulated GIP secretion, although GIP secretion itself in response to fat stimulation was unchanged (Morgan *et al.* 1983).

An exaggerated plasma GIP response to oral glucose has been seen in volunteers after a longer period (35 d) of high-fat feeding in man (Morgan *et al.* 1988*a*). This was not accompanied however, by any change in insulin secretion to the glucose load even though glucose tolerance was improved by the diet, in contrast to what has been observed in similar studies in animals (Hampton *et al.* 1983; Collier *et al.* 1985). A possible explanation for the improved glucose tolerance lies in the increase in glucose-stimulated GIP secretion induced by the diet. GIP has recently been shown to augment insulin-dependent inhibition of hepatic glycogenolysis both in rodents (Hartmann *et al.* 1986) and in man (Elahi *et al.* 1986). Consequently, the higher circulating GIP levels induced by glucose during high-fat feeding may serve to decrease glycogenolysis, which has been postulated to account for at least some of the glucose released into the general circulation after glucose ingestion. Although endogenous hepatic glucose production is small after glucose ingestion in man (Jackson *et al.* 1986), it is nevertheless very sensitive to changes in insulin concentration (Rizza *et al.* 1981).

Another possibility is that high-fat feeding alters the extraction ratio of insulin during its passage through the liver to the site of sampling in the periphery, making its measurement there an even more unreliable index of the actual rate of insulin secretion by the pancreas than we now know it to be (Hampton *et al.* 1986).

Hyperinsulinaemia is implicated as a risk factor in the development of cardiovascular disease. Current epidemiological research into diet and the incidence of cardiovascular disease has led to the recommendations to reduce dietary fat intakes (Committee on Medical Aspects of Food Policy, 1984). If hyperinsulinaemia can indeed be caused by an overactive entero-insular axis, is it possible to down-regulate its contribution to the circulating plasma insulin concentration by reducing fat intake in the diet? Evidence to support this possibility comes from the observation of an attentuation of the GIP response to an oral fat load in healthy human volunteers after they had consumed a low-fat diet for 35 d (Morgan *et al.* 1988*b*).

The demonstration that GIP secretion can be modified by both dietary changes and by hyperglycaemia, probably through a delaying effect on gastric emptying (Morgan *et al.* 1988*b*), suggests a mechanism whereby the extent of the hyperinsulinaemia that occurs in response to meals, its modification by dietary changes and its association with the pathology of various hyperinsulinaemic states may occur.

Developmentally the entero-insular axis in humans appears to begin to function within the first few weeks of birth (Lucas *et al.* 1980) and there is evidence that dietary manipulation can affect gastrointestinal hormones and insulin secretion from the earliest stages of development. Pre-term infants receiving milk feeds as a continuous infusion as opposed to intermittent amounts, for example, were found to have higher circulating GIP, gastrin and insulin levels by 13 d of age (Aynsley-Green *et al.* 1982). Thus early changes in the entero-insular axis induced by diet may play a role in the development of an individual's capacity to secrete insulin, possibly for the rest of their life. This is an area of nutrition that has hitherto been largely ignored, but which may be relevant to the development of various disorders in later life.

ACTION OF NUTRIENTS AND ENTERO-INSULAR STIMULI ON PANCREATIC β-CELLS

Nutrient ingestion and absorption generates a plethora of potential nutrient and non-nutrient stimuli to the pancreatic β-cells. Thus far, attention has been given mainly to those humoral mediators that originate within the gut. In this section we will consider how they interact at the level of the β-cell with the more conventional stimuli to insulin secretion, i.e. glucose and amino acids.

In general entero-insular stimuli amplify the insulin response of the β-cells to nutrient stimulation but their effectiveness is critically dependent on the prevailing arterial blood glucose level. Thus glucose modulates β-cell responsiveness to virtually all stimuli. Consequently the insulin secretory response is minimal at sub-threshold glucose concentrations, but is increasingly amplified by hyperglycaemia such as that encountered after consumption of a carbohydrate-containing meal (Gerich *et al.* 1976).

Several intracellular messengers have been ascribed key roles in the stimulation of insulin secretion. These include cytoplasmic Ca^{2+} ions, cyclic AMP formed by activation of adenylate cyclase and two products generated following activation of phospholipase C (Ins-1,4,5,-P_3 and diacylglycerol) (Sharp, 1979; Herchuelz & Malaisse, 1981; Wollheim & Sharp, 1981; Hellman, 1986; Henquin, 1987; Turk *et al.* 1987). Cytoplasmic Ca^{2+} is recognized as the principal regulator of insulin secretion (Hellman, 1986; Turk *et al.* 1987). Whereas glucose and other nutrients (e.g. certain amino acids) are thought to stimulate insulin secretion primarily by increasing cytoplasmic Ca^{2+} (Henquin, 1987), neural and hormonal entero-insular stimuli appear to amplify insulin secretion through direct intracellular activation of adenylate cyclase or phospholipase C (Hellman, 1986; Turk *et al.* 1987).

ACTIONS OF NUTRIENTS

Glucose and other sugars

Glucose is the only dietary sugar with the ability to stimulate insulin secretion from the pancreatic β-cells by direct action (Ashcroft, 1980; Malaisse, 1983) although others such as galactose and those yielding glucose on hydrolysis, such as sucrose, elicit an insulin response following activation of the entero-insular axis in addition to any hyperglycaemia they may themselves produce. In view of the crucial role of glucose in modulating the insulinotropic potency of other stimulators, but mainly because of its direct stimulatory effect, its mechanism of action on the secretory behaviour of pancreatic β-cells has been extensively investigated (Wollheim & Sharp, 1981; Malaisse, 1983; Hellman, 1986; Henquin, 1987; Petersen & Findley, 1987).

It is now established that the insulin-releasing effect of glucose (like that of mannose) stems from the ability of the pancreatic β-cells to transport and metabolize it (Ashcroft, 1980; Malaisse, 1983). Recent patch-clamp studies of ATP-sensitive K^+ channels in the β-cell plasma membrane (Ashcroft *et al.* 1984; Cook & Hales, 1984; Rorsman & Trube, 1985) suggest that a major action of glucose is to decrease K^+ permeability, and thereby depolarize the membrane with the opening of voltage-dependant Ca^{2+} channels (Hellman, 1986; Henquin, 1987; Petersen & Findley, 1987). The resulting influx of Ca^{2+} leads to elevation of cytoplasmic Ca^{2+} and is followed by repolarization. In the presence of a continuing glucose stimulus, the repolarization is followed by successive cycles of depolarization–repolarization, with corresponding episodes of Ca^{2+} influx which are coupled to extrusion of preformed insulin from the β-granules into the extracellular space and ultimately the circulation. At very-high glucose concentrations (> 16 mmol/l) the β-cell membrane remains depolarized for longer periods, with continuous spike activity as Ca^{2+} enters the cell and insulin discharge is sustained (Hellman, 1986; Henquin, 1987; Petersen & Findlay, 1987).

Amino acids

Several amino acids stimulate insulin secretion by direct action on the β-cells in vitro or when infused in vivo (Gerich *et al.* 1976). Considerable differences exist, however, in both their potencies and mechanisms through which they ultimately increase intracellular Ca^{2+} in order to trigger exocytosis (Henquin, 1987). Leucine, arginine and lysine are considered to be the most potent stimulators, but alanine, glycine, tryptophan, aspartate, isoleucine, asparagine, valine and phenylalanine have also been reported to exert stimulatory effects (Gerich *et al.* 1976). The physiological relevance of these pharmacological effects is still far from established and in vitro only leucine is capable of stimulating insulin secretion in the absence of glucose from the medium (Henquin & Meissner, 1981, 1986). Thus any insulinotropic action by amino acids is likely to depend on conjoint stimulation of β-cell function with glucose and the various entero-insular stimuli. Furthermore, since many amino acids are potent stimulators of pancreatic α_2-cells, glucagon secretion (Gerich *et al.* 1976) and activation of β-cell adenylate cyclase by glucagon, with the production of cyclic AMP, may augment any direct actions such amino acids may have on the β-cells themselves.

Recent detailed studies using leucine, arginine, lysine and alanine have demonstrated three basic mechanisms which appear to underlie the effects of amino acids on insulin release (Hellman *et al.* 1971; Henquin & Meissner, 1981, 1986; Charles & Henquin, 1983; Henquin, 1987). Leucine is transported into the β-cells where it is efficiently metabolized, giving rise to qualitatively similar changes in membrane potential and ionic fluxes as described for glucose. The effects of arginine and lysine on insulin release are quite different in so far as they are not metabolized by the β-cells but enter them through a transport system specific for cationic amino acids. This in turn leads to depolarization of the β-cell membrane and opening of voltage-dependent Ca^{2+} channels with Ca^{2+} influx. In contrast to leucine, arginine and lysine, alanine is only a weak stimulator of insulin release and is poorly metabolized by β-cells. It increases cytoplasmic Ca^{2+} by virtue of interference with Na^+ influx (Henquin, 1987).

Free fatty acids and ketone bodies

Certain free fatty acids and ketone bodies can exert modest stimulatory effects on β-cell function in the presence of glucose, at least in some species. Thus high concentrations of short-chain fatty acids (butyrate, octanoate, propionate and valerate), long-chain fatty acids (oleate and palmitate) and ketone bodies (acetoacetate and 3-hydroxybutyrate) have been reported to stimulate insulin release acutely in the rat, sheep and dog (Gerich *et al.* 1976). Relatively little effort has, however, been devoted to elucidation of the mechanisms involved. Presumably, the insulin-releasing effect of these agents stems from the ability of the β-cells to metabolize them. However, experiments in vitro suggest no simple relationship between the relative oxidation potential of the various ketone bodies and their abilities to stimulate insulin release (Biden & Taylor, 1983).

Other nutrients

Ingested minerals, vitamins and trace elements appear to have no major acute physiological effects on insulin secretion, although a possible role for calcium (Ca^{2+}) as a stimulator and modulator of entero-insular cells has received little attention up until now. It is, however, unlikely that the small changes in plasma Ca^{2+} that ordinarily follow ingestion of normal foods could have any significant regulatory effect on β-cell function directly.

ACTIONS OF ENTERO-INSULAR STIMULI

Neurotransmitter agents

Experiments involving the transplantation of denervated islets into diabetic recipients do not suggest a major role of neural innervation in the insulin response to feeding (Federlin & Bretzel, 1986). Nevertheless cholinergic activation is thought normally to contribute to the stimulus-secretion coupling process. Consistent with this view are the facts that resection and electrical stimulation of the vagus nerve have opposite effects on insulin secretion, and the classical cholinergic neurotransmitter, acetylcholine, augments insulin secretion in a glucose-dependent manner (Woods & Porte, 1974; Gerich *et al.* 1976; Wood *et al.* 1983; Ahren *et al.* 1986). Although the mechanism of action of cholinergic agents remained elusive for some time (Wollheim & Sharp, 1981), it has recently been established that they bind to muscarinic receptors on the β-cell membrane (Ostenson & Grill, 1987) and activate phospholipase C (Turk *et al.* 1987). In addition to this direct action on β-cells, cholinergic agents further amplify insulin release by stimulation of pancreatic α_2-cell glucagon secretion (Gerich *et al.* 1976) which serves as a paracrine stimulus to activate adenylate cyclase and increase cyclic AMP within the nearby β-cells. Although still somewhat speculative, cholinergic activation may also be associated with the release of insulinotropic peptides from peptidergic nerve terminals containing CCK, GRP, neurotensin or VIP.

Hormones

Interpretation of the findings implicating the various gastrointestinal hormones mentioned earlier in this review in the control of insulin secretion is complicated by many factors including species differences, peptide impurity, peptide instability, loss of functional receptors on collagenase-isolated islet cells and the use of supraphysiological concentrations in both in vitro and in vivo studies. Furthermore, the comparatively-recent discovery, and relative scarcity, of some of the peptides thought to be involved means that caution must be used in interpreting the results of the necessarily-limited number of studies that have been carried out so far. Thus the significance and mode of action has been established for only a small number of the potential entero-insular hormones. It has been clearly demonstrated, in the cases of glucagon, GLP-$1_{7\text{-}36}$ and GIP, that they all bind to specific receptors on the β-cells and activate adenylate cyclase leading to accumulation of cyclic AMP (Sharp, 1979; Szecowka *et al.* 1982; Korman *et al.* 1985; Altman *et al.* 1987; Drucker *et al.* 1987). CCK (and its active fragments) on the other hand binds to another specific species of receptor which activates phospholipase C leading to the generation of inositol-1,4,5-triphosphate and diacylglycerol in β-cells (Best & Malaisse 1983; Versphol *et al.* 1986; Turk *et al.* 1987; Zawalich *et al.* 1987). Both sets of second messengers amplify the Ca^{2+} signal for exocytosis, although in different ways to each other.

The entero-insular hormones therefore appear to exploit both the known amplification systems for insulin release and it is likely that other less-well-researched hormones also employ one of these two mechanisms. It is also possible, due to notable sequence homologies, that some receptors will bind more than one peptide, albeit with different affinities. Bearing these points in mind it is possible to conclude that secretin and GHRF work by activating adenylate cyclase (Green *et al.* 1986; Kofod *et al.* 1986). However, the mode of action of other insulin-stimulatory hormones of the gastrointestinal tract, notably VIP and neurotensin remains to be established, and their importance in the physiological regulation of of insulin secretion is still far from certain. In djungarian hamsters, intestinal and plasma GIP are increased (Bailey & Flatt, 1988*a*).

ROLE OF THE ENTERO-INSULAR AXIS IN DISEASE

Because of the evidence implicating the entero-insular axis in augmentation of the direct effects of nutrients on insulin secretion, it is pertinent to consider its role in the pathogenesis of disease associated with insulin deficiency and excess. In the following we review the possible role of the entero-insular axis in diabetes and obesity, two conditions of disordered insulin secretion in which dietary factors have been shown to play an important part.

ANIMAL STUDIES

Considerable evidence has accumulated linking diet and the entero-insular axis with the obesity–diabetes syndromes of rodents (Flatt *et al.* 1984; Bailey & Flatt, 1986, 1988*a*). These animal models, in common with human subjects showing NIDDM, exhibit hyperinsulinaemia, insulin resistance and glucose intolerance (Bray & York, 1979; Bailey & Flatt, 1986).

One extensively-studied model is the genetically-obese hyperglycaemic (*ob/ob*) mouse. These mutant mice exhibit hyperphagia and obesity, as well as the disordered insulin secretion and action described previously. Short-term fasting and refeeding experiments in these mice have shown that proteins and fats, but especially carbohydrates, are powerful insulin secretagogues when taken by mouth (Flatt & Bailey 1982*b*; Flatt *et al.* 1984) but that parenteral glucose has little insulinotropic effect (Flatt & Bailey 1981*a*). This clear dependence of the insulin-releasing action of glucose on route of administration suggests that neural and hormonal pathways, triggered by ingestion of glucose and other nutrients, are important mediators of the hyperinsulinaemia (Flatt & Bailey 1981*b*). Consistent with this view is the observation that *ob/ob* mice exhibit generalized entero-endocrine cell hyperplasia (Polak *et al.* 1975; Best *et al.* 1977). Exaggerated plasma insulin responses have also been observed to many of their secretory products, e.g. GIP, glucagon, GLP-1, bombesin (GRP), CCK (peptide sequences 1–33 and 1–8), neurotensin, opiate peptides and GHRF as well as to adrenocorticotrophic hormone and the cholinergic agent, pilocarpine (Flatt & Bailey 1982*a*, 1987; Flatt *et al.* 1982, 1984; Bailey & Flatt, 1984, 1987*a*, *b*, *c*; 1988*b*). Hyperplasia of the intestinal GIP-secreting K-cells, is particularly marked in *ob/ob* mice, as are the increases in GIP concentrations in the intestines and plasma which result in part from hyperalimentation and impaired suppression of GIP secretion by insulin (Flatt *et al.* 1983, 1984, 1985). The role of GIP in the insulin-secretory response to feeding in this animal model is further highlighted by the exaggerated effect on circulating GIP levels of feeding glucose, amino acids or fatty acids (Flatt *et al.* 1984; Kwasowski *et al.* 1985), the mirroring of age-changes of plasma insulin by alterations in circulating GIP levels (Flatt *et al.* 1984) and the equally-profound depressant effect on each of them of short-term food withdrawal (Flatt & Bailey 1984*a*; Flatt *et al.* 1984). Particularly noteworthy is the ability in young *ob/ob* mice on high-fat diets to induce an increase in K-cell number, intestinal GIP content and circulating GIP concentrations (Bailey *et al.* 1986*b*).

Other animal models of obesity–diabetes, for example, diabetes-obese (*db/db*) mice exhibit a more-specific entero-endocrine cell hyperplasia, where intestinal GIP and neurotensin concentrations are raised, but those of VIP, GRP, substance P and neurokinin A are unchanged (Flatt *et al.* 1983; Sheppard *et al.* 1985; Bailey *et al.* 1986*a*). Zucker fatty (*fa/fa*) rats have only slightly increased plasma insulin levels with no obvious change in circulating GIP concentrations (Morgan, 1979; Chan *et al.* 1984). They do, however, exhibit increased sensitivity to the insulin-releasing action of GIP (Chan *et al.* 1984) and its action on fatty acid incorporation into adipose tissue (Beck & Max, 1986).

CLINICAL STUDIES

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. Epidemiological studies have indicated a strong dietary component in the development of NIDDM and linked the consumption of a high-fat low-carbohydrate diet with an increased prevalence of the disease (Himsworth, 1935; West & Kalbfleisch, 1971). Diets low in carbohydrate and high in fat improve glucose tolerance acutely, and have been widely used in the past in the treatment of diabetics (Truswell & Thomas, 1975) but more recent studies have demonstrated that habitually-increased fat consumption decreases insulin sensitivity (Beck-Neilson *et al.* 1980).

Most entero-insular axis studies in diabetics have centred around GIP, but with conflicting results. Some investigators reported finding exaggerated GIP responses to nutrient ingestion (Ross *et al.* 1977; Salera *et al.* 1982) whilst others reported them as similar to, or less than, those of lean healthy subjects (Alam & Buchanan, 1980; Levitt *et al.* 1980). In one large series a biomodal distribution of GIP secretion after oral glucose was found, demonstrating hyper- as well as hyposecretion (Creutzfeldt *et al.* 1983). Most recent studies of patients with IDDM have not revealed any abnormalities of GIP release (Service *et al.* 1984) or differences in the molecular forms of GIP secreted in response to nutrients (Krarup *et al.* 1987).

A reduced contribution of the entero-insular axis to insulin secretion in response to oral glucose has been demonstrated in patients with NIDDM (Nauck *et al.* 1986). Changes in GIP secretion are not necessarily synonymous with changes in the entero-insular axis, but a reduced effect of exogenous GIP on insulin secretion has also been described in NIDDM, suggesting a decreased sensitivity of the β-cell to GIP stimulation (Ross *et al.* 1974; Krarup *et al.* 1984).

Exogenous insulin administered therapeutically in excess to human diabetics can cause obesity (Marks & Davison, 1976) and hyperinsulinaemia is the most characteristic biochemical anomaly in seemingly-otherwise-healthy obese subjects. Restriction of food intake by obese individuals reduces their exaggerated insulinaemic responses to various stimuli long before significant changes in body-weight become apparent, suggesting that food intake is an important determining factor in their hyperinsulinaemia. This link, between food intake and disordered insulin secretion, implies a correspondingly-deranged entero-insular axis and subsequent work has implicated GIP in the pathogenesis of the hyperinsulinaemia of human obesity.

Extensive studies by Creutzfeldt *et al.* (1978) on obese human subjects, with and without diabetes, have shown that their GIP responses to oral nutrients, particularly fat, are exaggerated. The exaggerated insulin response to oral glucose by obese subjects was reduced by weight loss and was accompanied by a reduced GIP response.

Studies using combined glucose and fat loads suggest that feedback control by endogenous insulin of GIP secretion is defective in obesity (Ebert *et al.* 1979). The same group have shown that the GIP response to a test meal in obese subjects is reduced after 5 d of food restriction and is accompanied by an improvement in glucose tolerance (Willms *et al.* 1978). These findings bear a striking similarity to the pattern of GIP secretion observed in animals and man after they have consumed a high-fat diet for some time and may indicate a causal relationship (Hampton *et al.* 1983; Morgan *et al.* 1983, 1988*a*).

Most subsequent workers have confirmed that GIP responses to nutrient ingestion are increased by obesity (Deschamps *et al.* 1980; Salera *et al.* 1982; Sirinek *et al.* 1986), although some have found similar (Amland *et al.* 1985) or even smaller (Service *et al.* 1984) responses than in lean healthy subjects. These discrepancies may be due to differences in the

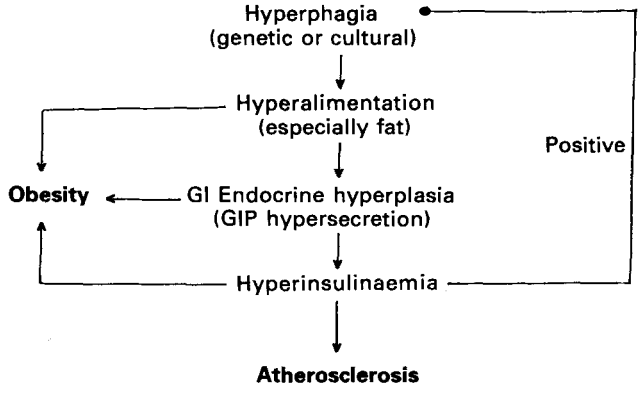

Fig. 1. Postulated sequence for the involvement of gastrointestinal (GI) hormones in the development of obesity and atherosclerosis. GIP, gastric inhibitory peptide.

habitual diets of the obese subjects, particularly, if they have been involved in attempts at weight reduction, a factor which has been ignored in the past.

The activation of adipose-tissue lipoprotein lipase by GIP (Eckel *et al.* 1978) promoting lipogenesis and lipid deposition in adipose tissue implicates GIP in a dual role in human obesity, promoting fat deposition directly in addition to its contribution to the pathogenesis of the observed hyperinsulinaemia.

CONCLUSIONS

The entero-insular axis makes a considerable contribution to total insulin secretion and the demonstration that gastrointestinal hormone secretion can be modified by dietary manipulation has important implications in our understanding of pathology of diseases such as atherosclerosis, obesity, NIDDM and even IDDM in which insulin secretion is disordered. This is illustrated by the role we postulate for GIP in the production and maintenance of obesity.

GIP is an anabolic hormone which is secreted during the absorption of food. It stimulates the release of insulin in the presence of mild to moderate hyperglycaemia, such as that which follows the ingestion of a mixed meal, and it favours the uptake of exogenous fat by adipose tissue. GIP production is increased in obese subjects and experimental animals. It is postulated that a hormone possessing GIP properties would be expected to favour the development of obesity in hyperalimented subjects, with the consequent sequels of insulin resistance and increased incidence of atherosclerosis characteristic of the obese, as shown in Fig. 1. The induction of GIP hypersecretion by long-term high-fat feeding and the loss of feedback control by insulin might account for the otherwise-inexplicable hyperinsulinaemia observed in symptomatic and asymptomatic atherosclerotic subjects in whom it is believed to play a causal role in the pathogenesis of their myocardial ischaemia.

GIP-induced insulin secretion forms just one part of the entero-insular axis which has such a pronounced effect on all aspects of metabolism. Other gastrointestinal hormones, notably GLP-1 (peptide sequence 7–42) and CCK are also implicated and other, yet unidentified, gut peptides may also contribute. These are exciting new areas which are just beginning to be explored. Our knowledge of the precise mechanism of action of the various insulin-stimulating gastrointestinal hormones and peptides at pancreatic β-cell level is far

from complete. It is, however, an area essential to our understanding of the entero-insular axis, and elucidation of the interaction of nutrients and gastrointestinal hormones at this level should prove rewarding.

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