

Nutrient-induced secretion and metabolic effects of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1

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Sécrétion induite par les nutriments et effets métaboliques du polypeptide insulinothropique dépendant du glucose et du peptide 1 semblable au glucagon

RÉSUMÉ

Le GIP (polypeptide insulinothropique dépendant du glucose) et le GLP-1(7-36)amide (forme tronquée biologiquement active du peptide 1 semblable au glucagon) sont tous deux des hormones de la muqueuse intestinale, situées respectivement dans l'intestin grêle proximal, et dans l'intestin grêle distal et le côlon. Aussi bien le GIP que le GLP-1(7-36)amide sont sécrétés en réponse aux nutriments. Dans le cas du GIP, l'absorption des nutriments est un prérequis pour la sécrétion hormonale, mais ceci ne semble pas être nécessaire pour la sécrétion du GLP-1(7-36)amide. Chez l'homme, les graisses sont le stimulus le plus puissant pour la sécrétion de GIP, et les glucides le stimulus le plus puissant pour la sécrétion de GLP-1(7-36)amide. Ceci est directement en contradiction avec nos observations chez les rongeurs et le porc. On ne sait pas s'il s'agit d'une véritable différence d'espèces dans la réponse adaptative au régime habituel, mais les modifications (augmentation de la consommation des graisses) aussi bien chez le rat que chez l'homme peuvent augmenter les niveaux du GIP dans le plasma. Les repas de nutriments mixtes (qui sont plus représentatifs des apports alimentaires normaux) sont des stimulants puissants de la sécrétion de GIP et de GLP-1(7-36)amide dans toutes les espèces étudiées. Le GIP tout comme le GLP-1(7-36)amide sont des stimulants physiologiques de la sécrétion postprandiale d'insuline et peuvent interagir pour stimuler l'insuline de manière additionnelle. L'action du GLP-1(7-36)amide sur la cellule β du pancréas est plus puissante que celle du GIP, en termes molaires, mais ceci reflète des niveaux circulants de GLP-1(7-36)amide moins importants. Les profils de sécrétion de ces hormones sur 24 h et l'identification de récepteurs dans les tissus autres que le pancréas suggèrent que ces hormones pourraient avoir d'autres rôles métaboliques en plus de leurs effets sur la sécrétion de l'insuline. Nous avons étudié les effets du GIP et du GLP-1(7-36)amide dans le tissu adipeux et nous avons montré que le GIP peut, comme l'insuline, stimuler directement la lipoprotéine lipase (EC 3.1.1.34; LPL) dans des explants de tissu adipeux du rat. Le GLP-1(7-36)amide dans la même gamme de concentrations que le GIP est cependant sans effet sur l'activité de la LPL. En utilisant la même technique expérimentale aussi bien le GIP que le GLP-1(7-36)amide se sont révélés stimuler la lipogénèse *de novo*. Les implications de ce travail sur l'obésité, le NIDDM et la maladie coronarienne du coeur sont étudiées. En résumé, aussi bien le GIP que le GLP-1(7-36)amide exercent une influence indirecte sur le métabolisme

postprandial par leur action sur la sécrétion de l'insuline. Ils peuvent également exercer une influence directe par leur action sur le métabolisme du tissu adipeux. Le GIP et le GLP-1(7-36)amide peuvent donc influencer l'élimination des métabolites après les repas, et il est possible qu'ils jouent un rôle dans l'acheminement des substrats. Les récepteurs spécifiques du GIP et du GLP-1(7-36)amide ont été repérés dans différents tissus, et à ce jour on ne peut que spéculer sur leur fonction. Il est essentiel d'étudier les actions de ces hormones sur les événements métaboliques à l'extérieur de l'intestin pour que nous comprenions les processus physiologiques aussi bien que pathologiques qui sont influencés par le type d'alimentation.

The ongoing discovery of new gut hormones or new biological actions for old hormones encourages reassessment of their functions. The gut is the body's largest endocrine organ both in terms of organ size and the range of peptide hormones it produces. The actions of gut peptides can be broadly subdivided into three groups according to their modes and sites of action. First, some gut hormones act locally (within the gut) influencing gastric, pancreatic and biliary secretion, gut motility and gut mucosal proliferation. Second, a neuro-endocrine role within the nervous system is being elucidated for some gut hormones, notably in satiety regulation. A third action of gut hormones is beyond the gut, influencing postprandial metabolism. This endocrine action may be direct or indirect through stimulation of other hormones, most notably insulin. Individual gut hormones are not exclusive in their actions. Glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide (GLP)-1(7-36)amide (the biologically-active truncated form of GLP-1) have physiological actions both within the confines of the gut and beyond the gut. Both GIP and GLP-1(7-36)amide are secreted in response to nutrient ingestion and are potent stimulators of glucose-induced insulin secretion (Kreymann *et al.* 1987). Research has previously centred on a role for GIP and GLP-1(7-36)amide in carbohydrate metabolism, but evidence is also accumulating for a role of these hormones in lipid metabolism. The full biological actions of these two hormones remain to be elucidated; however, their receptors have been found in a range of tissues, including adipose tissue. The present review will explore the actions of GIP and GLP-1(7-36)amide outside the gut; in particular, their role in postprandial lipid metabolism.

STRUCTURE AND OCCURRENCE OF GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE AND GLUCAGON-LIKE PEPTIDE-1

GIP and GLP-1(7-36)amide are structurally-related members of the secretin family of gastrointestinal peptides. Porcine, human and bovine GIP have been shown to consist of forty-two amino acid residues (Jörnvall *et al.* 1981; Moody *et al.* 1984) compared with the thirty amino acid residues of GLP-1(7-36)amide. The sequence homology is especially strong at the N-terminal, GLP-1(7-36)amide is identical to GIP in eight of eleven residues (Schmidt *et al.* 1985). It has been shown for both peptides that an intact N-terminus is essential for biological activity (Mentlein *et al.* 1993).

GIP-secreting K cells are located exclusively in the small intestine, being concentrated mainly in the duodenum and upper jejunum of man (Bloom & Polak, 1981), although in rodents K cells are as numerous in the ileum as in the upper small intestine (Solcia *et al.*

1989). In man, GIP-release studies in response to glucose stimulation have confirmed the proximal small intestine to be the major, but not exclusive site of endogenous GIP release, as small quantities of GIP are also released by the distal small intestine (Thomas *et al.* 1977).

GLP-1(7-36)amide is produced in the mucosal L cell (Varndell *et al.* 1985) from proglucagon. Highest concentrations of this hormone have been isolated from the terminal ileum and colon in rats (Kreymann *et al.* 1988); however, significant amounts of oxyntomodulin (another hormone produced in the intestine from the same precursor molecule as GLP-1; for reviews, see Conlon, 1988; Holst, 1994) have been found in the jejunum and caecum (Kervran *et al.* 1987). The localization of GLP-1(7-36)amide in the distal ileum and colon is at odds with a proposed role for this hormone in postprandial metabolism, especially a role in stimulating insulin secretion. Yet, despite its location, rapid increments in plasma GLP-1(7-36)amide levels have been observed in response to nutrient ingestion. It has been suggested that small amounts of nutrients do reach the distal small intestine rapidly after digestion and this is supported by studies in patients with accelerated gastric emptying rates (Miholic *et al.* 1991). Alternatively, a novel entero-endocrine loop between GIP and GLP-1(7-36)amide has been proposed, as the intravenous infusion of GIP induces a rise in plasma GLP-1(7-37), the biologically-active unamidated form of GLP-1 (Roberge & Brubaker, 1993).

EFFECT OF NUTRIENTS ON GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE AND GLUCAGON-LIKE PEPTIDE-1(7-36)AMIDE STIMULATION

Carbohydrates

GIP is secreted in response to the active absorption of nutrients. Monocomponent perfusion studies in rats have shown that sugars which are actively transported by the Na-dependent hexose pathway stimulate GIP secretion (Sykes *et al.* 1980). Studies in pigs fitted with mesenteric arterial and hepatic portal cannulas have shown that the rate of GIP secretion is proportional to the rate of glucose absorption from the gut (Ellis *et al.* 1995). The nature and mechanism of the nutrient stimulus for GLP-1(7-36)amide secretion is not so clear. Interpretation of the data is made difficult by the low circulating levels of this hormone and different cross-reactivities of antisera with the various biologically-active and inactive forms of GLP-1. Glucose is a stimulus for GLP-1 secretion in porcine ileum (Ørskov *et al.* 1986) and in man (Kreymann *et al.* 1987). It has been suggested from observations in dogs that digestion may not be a prerequisite for GLP-1(7-36)amide secretion provided that specific steric requirements of sugars are met (Shima *et al.* 1991). Measurement of plasma GIP and GLP-1(7-36)amide in man after sucrose ingestion supports a mechanism of secretion of GLP-1(7-36)amide in response to the presence of sucrose in the intestine; this contrasts with the stimulation of GIP secretion by the absorption product (glucose) (Fukase *et al.* 1992).

Fat

As with sugars, absorption of fatty acids is a necessary prerequisite for their effect on GIP secretion. Long-chain triacylglycerols stimulate GIP, an increase in fatty acid chain length and a greater degree of unsaturation enhancing GIP release (Kwasowski *et al.* 1985). Fish oils are very potent stimuli for GIP secretion (Lardinois *et al.* 1988). Only

fatty acids that are re-esterified in the enterocyte and incorporated into chylomicrons stimulate GIP secretion. It has been postulated that the energy-requiring re-esterification process may be the signal for GIP secretion (Thomson & Dietschy, 1981) based on the observation that only actively-absorbed sugars stimulate GIP, the energy requirement being a common link between nutrients and stimulation. Recently, it has been reported that not all long-chain fatty acids absorbed from a single meal are released into the circulation postprandially, but are stored and released following a subsequent meal (Fielding *et al.* 1995). In man there is a good concordance between plasma triacylglycerol and plasma GIP levels postprandially, allowing us to hypothesize that chylomicron release from the enterocyte rather than re-esterification of triacylglycerols within the enterocyte stimulates GIP release. On an energy basis, in man, fat is a more potent stimulus for GIP secretion than glucose (Brown *et al.* 1975; Falko *et al.* 1975; Penman *et al.* 1981; Jorde *et al.* 1985). A monocomponent fat test meal produces a small but significant rise in circulating plasma GLP-1(7-36)amide concentrations in man (Elliott *et al.* 1993). Again the mechanism of stimulus-secretion coupling for GLP-1(7-36)amide is unknown.

Protein

Protein is a poor stimulus for GIP secretion. In man, intraduodenal administration of a mixture of amino acids (i.e. arginine, histidine, isoleucine, lysine and threonine) produces a marked rise in GIP (Thomas *et al.* 1978). In contrast, in mice, individual amino acids produce modest and transient GIP increases with no difference in potency between the amino acids tested (Flatt *et al.* 1991). Use of whole protein (280 g fillet steak or 45 g meat extract) failed to produce a significant elevation in serum GIP levels in man (Cleator & Gourley, 1975). Plasma GLP-1(7-36)amide is significantly but only transiently increased by a monocomponent protein test meal (Elliott *et al.* 1993).

Mixed meals

Interpretation of data relating nutrient ingestion to secretion of gastrointestinal hormones is confounded by the differential effects that different nutrients, the volume and physical form of the food exert on gastric emptying (Low, 1990). Additionally macronutrients are rarely ingested alone, more usually they are consumed in combination in a complex meal form.

We have recently studied the effects of carbohydrate and fat, alone and in combination, on both GIP and GLP-1(7-36)amide secretion in the growing pig (Knapper *et al.* 1995b). Nutrients were infused intraduodenally to eliminate any differential effects of gastric emptying, at an infusion rate which reflected the rate of gastric emptying in pigs after a mixed meal. In contrast to our observations in human subjects, fat was the most potent stimulus for GLP-1(7-36)amide secretion and carbohydrate for GIP secretion. However, a dual-nutrient infusion of carbohydrate and fat was the strongest stimulus for both GIP and GLP-1(7-36)amide secretion (Fig. 1). Also, we observed that plasma insulin levels were higher following glucose and fat administration than following glucose alone, and plasma triacylglycerol levels were attenuated following glucose and fat compared with fat infusion alone. These results are consistent with our hypothesis of a role for GIP and GLP-1(7-36)amide in the stimulation of insulin secretion and clearance of plasma triacylglycerol.

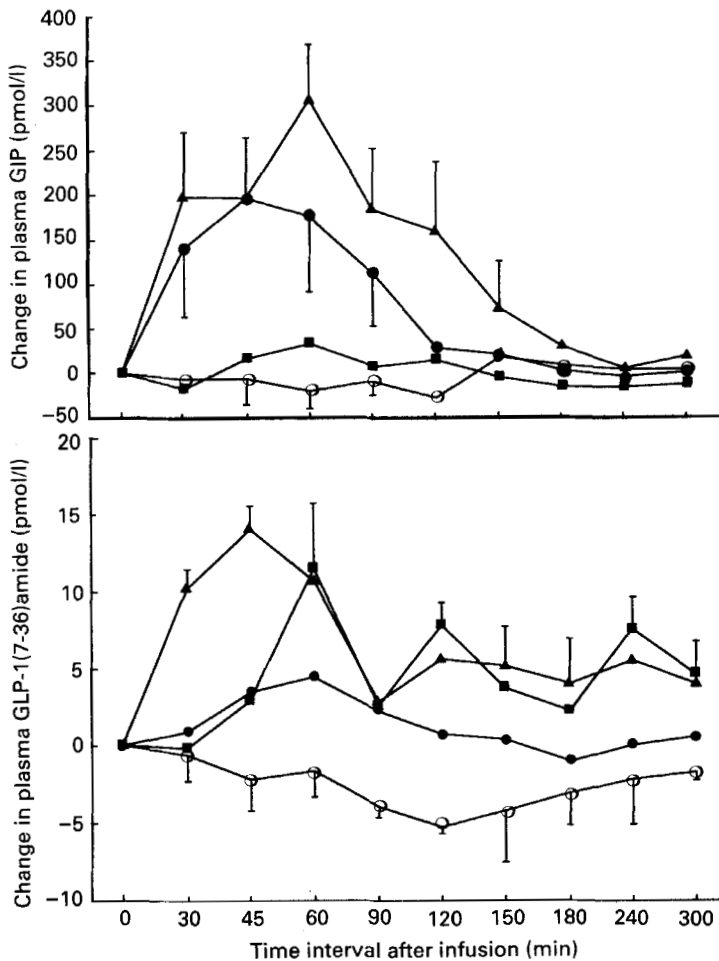


Fig. 1. Effect of intraduodenal infusion of (○) saline (9 g NaCl/l), (●) glucose (40 g), (■) fat (60 g), or (▲) glucose + fat (40 + 60 g) on plasma glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP)-1(7-36)amide in pigs. Values are means with their standard errors, represented by vertical bars for a minimum of three infusions for each nutrient.

EFFECTS OF NUTRIENTS: INNATE OR ADAPTIVE?

A typical Western diet provides 40% of the energy as fat; in comparison a laboratory rat obtains less than 10% of its dietary energy as fat. This habitual dietary difference may be an important factor in the observed species difference between rats and humans for the relative potency of fat or carbohydrate as stimuli for GIP secretion. Our observations in pigs that fat is a poor stimulus for GIP secretion is supported by an earlier study in pigs where mixed meals of varying fat content were infused (Ponter *et al.* 1991). The normal diet of commercial pigs, like rats, is low in fat.

Experimentally-induced changes in habitual diet can also influence gut hormone secretion over a period of time. Short-term (11 d) feeding of a high-fat diet to human volunteers causes no change in the GIP secretory response to a fat stimulus (Morgan

et al. 1983), but a longer period (35 d) of high-fat feeding (52% energy from fat) results in a small but significant increase in the GIP secretory response to oral glucose (Morgan *et al.* 1988). A similar result can be seen in other species, such as pigs (Ponter *et al.* 1991) and rats (Hampton *et al.* 1983). Obese hyperglycaemic (ob/ob) mice weaned at 3 weeks onto a high-fat cafeteria diet have an increased plasma and intestinal concentration of GIP by 11 weeks of age, together with an increased density of K cells in the upper jejunum (Bailey *et al.* 1986).

Recently, we compared plasma GIP responses to a mixed meal in a population of adult males resident in the UK (mean age 22.3 years) with responses of age-matched Greeks of Cretan and non-Cretan origin. All subjects consumed an average of 39% energy from fat, but the fatty acid profile of the diets differed as the Greeks consumed higher intakes of monounsaturated fatty acids and lower intakes of saturated fatty acids than the UK subjects. Significant differences in circulating GIP were found between the groups, with Greek subjects exhibiting higher fasting and postprandial GIP levels than their UK counterparts (Knapper *et al.* 1995a).

In summary, the amount of GIP and GLP-1(7-36)amide released is influenced in a complex manner by the type and amounts of nutrients ingested. In addition, there are clear indications of adaptive changes in the amplitude of the hormonal signal released in response to long-term diet exposure.

THE METABOLIC ACTIONS OF GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE AND GLUCAGON-LIKE PEPTIDE-1(7-36)AMIDE

The entero-insular axis (EIA)

In 1906 it was first suggested that oral administration of acid extracts of porcine proximal small intestine could modify the glycosuria of clinical diabetes mellitus (Moore *et al.* 1906). This observation provided early recognition that gastrointestinal hormones can act outside of the gastrointestinal tract. Unger & Eisentraut (1969) subsequently developed the term EIA to describe the regulatory control exerted by the gastrointestinal tract on the endocrine pancreas. Until the discovery of GLP-1(7-36)amide in the early 1980s (Bell *et al.* 1983), GIP was widely regarded as the major endocrine component of the EIA (Creutzfeldt & Ebert, 1985).

Both GIP and GLP-1(7-36)amide stimulate insulin secretion via the EIA under moderate hyperglycaemic conditions (for review, see Morgan, 1992), i.e. they potentiate glucose-induced insulin secretion. In rats the degree of glycaemia required has been assessed as a plasma glucose concentration greater than 5.5 mM (Anderson *et al.* 1978). GLP-1(7-36)amide is the more potent stimulus of insulin secretion in molar terms, exceeding the action of GIP by four- to sevenfold (Kreymann *et al.* 1987; Nauck *et al.* 1993). However, the fasting and postprandial circulating plasma concentrations of GLP-1(7-36)amide are much lower than those of GIP. Receptors for both hormones have been located on pancreatic B cells (Ørskov & Poulssen, 1991; Usdin *et al.* 1993). GIP and GLP-1(7-36)amide act primarily by increasing cyclic AMP concentration in the B cell (Drucker *et al.* 1987; Göke & Conlon, 1988; Göke *et al.* 1989; Szecowka *et al.* 1992); they can interact with each other in an additive manner at sub-maximal concentrations to achieve this result, thus supporting the concept of a common signal transduction pathway (Fehmann *et al.* 1990; Montrose-Rafizadeh *et al.* 1994).

Table 1. *Location of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP)-1(7-36)amide receptors*

	GIP	GLP-1(7-36)amide
Pancreas	+	+
Adipose tissue	+	+
Brain	+	+
Gut	+	+
Heart	+	
Adrenal cortex	+	
Pituitary	+	
Skeletal muscle		+
Kidneys		+
Lungs		+

Direct actions on other tissues

The B cells of the pancreas are not the only cells to express receptors to GIP and GLP-1(7-36)amide. GIP receptors have been located in several organs including adipose tissue (Usdin *et al.* 1993). Likewise GLP-1(7-36)amide receptors have been located in many tissues including adipose tissue (Merida *et al.* 1993; Valverde *et al.* 1993; Table 1). These discoveries suggest that the actions of these hormones may not be confined to modulating insulin secretion postprandially. The action of GIP and GLP-1(7-36)amide on adipose tissue metabolism has attracted increasing attention and it is this metabolic role on which we focus.

Measurement of 24 h profiles of GIP and GLP-1(7-36)amide in human subjects eating a typical Western-style diet of three main meals and three snacks per d and sleeping for 8 h at night demonstrated that the circulating profiles of these hormones differ markedly from the profiled insulin secretion (Fig. 2; Elliott *et al.* 1993). Insulin secretion peaks within 2 h of meal ingestion and returns to basal values between meals. In contrast GIP and GLP-1(7-36)amide levels are elevated for the duration of the day, only returning to basal levels during the overnight fasting period. However, the 24 h pattern of circulating gastrointestinal hormone levels closely parallels the circulating plasma triacylglycerol levels, an observation which supports the hypothesis that these hormones could be involved in dietary triacylglycerol disposal.

ACTIONS OF GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE AND GLUCAGON-LIKE PEPTIDE-1(7-36)AMIDE ON ADIPOSE TISSUE METABOLISM

Effects on lipoprotein lipase (EC 3.1.1.34; LPL)

Both exogenous and endogenous GIP lower postprandial plasma triacylglycerol levels following a fat load in rats (Ebert *et al.* 1991). Additionally GIP promotes the clearance of chylomicron triacylglycerol in dogs (Wasada *et al.* 1981). Adipose tissue LPL is a key regulatory enzyme in the hydrolysis of circulating dietary and endogenous triacylglycerol before uptake of liberated free fatty acids into adipose tissue. Using an explant technique (which preserves the endothelial architecture reflecting *in vivo* adipose tissue environment) we have demonstrated that GIP, at postprandial circulating concentrations, in

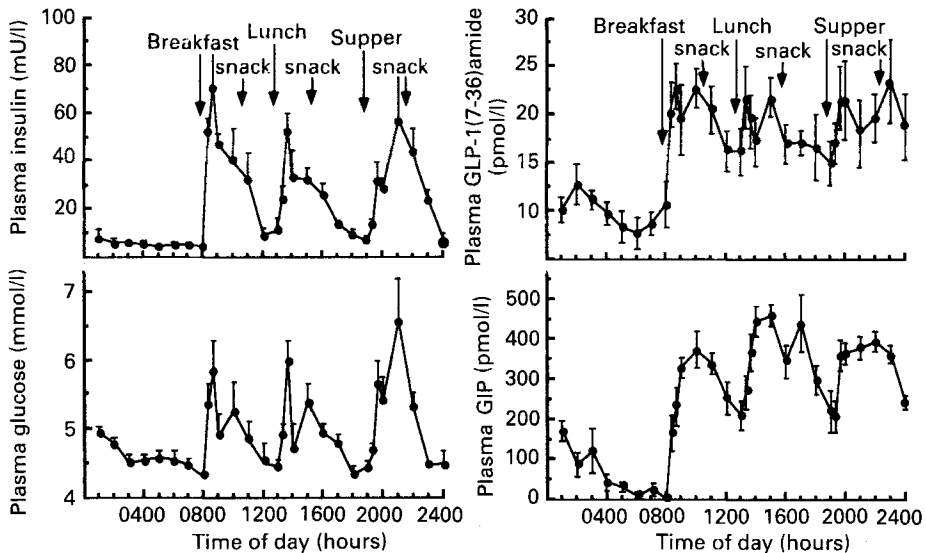


Fig. 2. Profiles (24 h) of plasma glucose, insulin, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP)-1(7-36)amide levels in healthy subjects consuming a normal diet. Values are means with their standard errors, represented by vertical bars, for six subjects.

common with insulin, directly stimulates heparin-releasable LPL activity in explants of rat adipose tissue (Knapper *et al.* 1995d). GLP-1(7-36)amide over the same concentration range as GIP was without effect on LPL activity (Fig. 3). In addition, GIP has been shown to stimulate the synthesis and release of LPL in cultured mouse pre-adipocytes (Eckel *et al.* 1979).

Diet modification can affect adipose tissue LPL activity; rats fed on a high-fat diet for 14 d have significantly higher basal and GIP- and insulin-stimulated adipose tissue LPL

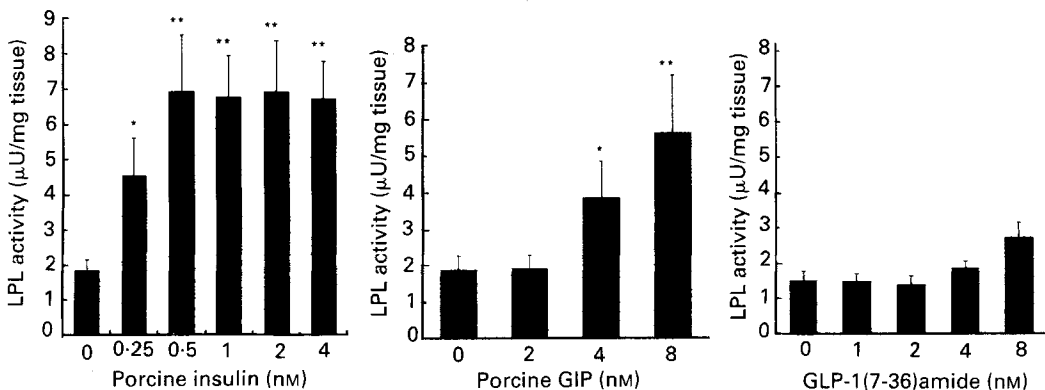


Fig. 3. Lipoprotein lipase (*EC* 3.1.1.34; LPL) activity in rat epididymal adipose tissue cultured with insulin, glucose-dependent insulinotropic polypeptide (GIP) or glucagon-like peptide (GLP)-1(7-36)amide. Values are means with their standard errors, represented by vertical bars, for ten to seventeen rats. Mean values were significantly different from basal values: * $P < 0.05$, ** $P < 0.01$.

activity than rats fed on a laboratory chow diet (Oben *et al.* 1991). In man acute ingestion of fish oils increases post-heparin plasma LPL activity and LPL mRNA levels (Murphy *et al.* 1993) and as mentioned previously fish oils are a potent stimulus for GIP secretion (Lardinois *et al.* 1988). Also, progressive parallel increases in postprandial heparin-releasable plasma LPL and plasma GIP have been observed in man following a series of mixed meals where meal volume was maintained but the fat content was increased over the range of 20–80 g (Murphy *et al.* 1995). A simultaneous increase in adipose tissue LPL activity and plasma GIP levels was observed in a subject with apolipoprotein CII deficiency (the cofactor for expression of LPL activity); both LPL activity and GIP concentration decreased after administration of apolipoprotein CII-rich plasma (Brunzell *et al.* 1983).

Effects on fatty acid synthesis

Both GIP and GLP-1(7-36)amide stimulate *de novo* lipogenesis in rat adipose tissue (Oben *et al.* 1991). This action was observed at physiological concentrations of both hormones, but at lower concentrations (0.1 nM) GLP-1(7-36)amide was the more potent stimulator of fatty acid synthesis (as measured by incorporation of [¹⁴C]acetate into saponifiable fat). We have recently reported a significant increase in intestinal GLP-1(7-36)amide concentration in small intestines of piglets at 33 d of age (12 d after weaning) when compared with 16-d-old suckling piglets (Knapper *et al.* 1995c). This observation is consistent with a role for GLP-1(7-36)amide in adipose tissue metabolism when glucose is the precursor for fat deposition.

Other effects on adipose tissue

In support of an anabolic role for GIP in adipose tissue metabolism, GIP has been shown to inhibit the lipolytic action of glucagon by competitive interaction with the glucagon receptor (Dupré *et al.* 1976; Ebert & Creutzfeldt, 1987).

Both GIP and GLP-1(7-36)amide, therefore, potentially offer a hormonal signal between nutrient intake and white adipose tissue, ensuring the rapid clearance of triacylglycerol from the circulation. This action could be considered very desirable as it returns the blood transport system to its basal state. However, a high-fat diet is known to be associated with or to exacerbate certain diseases and, thus, the actions of GIP and GLP-1(7-36)amide on adipose tissue metabolism may contribute to these pathological conditions.

RELATIONSHIP OF GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE AND GLUCAGON-LIKE PEPTIDE-1(7-36)AMIDE TO DISEASE

Obesity and non-insulin-dependent diabetes mellitus

An excess storage of fatty acids in adipose tissue produces the clinical condition, obesity. Obesity is caused by an excess of energy intake over expenditure, but the factors that regulate nutrient storage in adipose tissue and their relationship to nutrient supply are not well understood. Insulin has long been recognized as an important anabolic signal to adipose tissue, but insulin oversecretion by itself cannot explain the increased accretion of excess adipose tissue. Animal models of obesity-diabetes syndromes support a role for

an overactive EIA in the metabolic disturbance. The genetically-obese (ob/ob) mouse exhibits hyperplasia of intestinal GIP-secreting cells and circulating GIP and insulin levels are raised (Flatt *et al.* 1983). Circulating GLP-1(7-36)amide levels cannot be measured in reasonable blood volumes in these animals, but intestinal levels are elevated when compared with homozygous lean littermates and these animals can respond to exogenous GLP-1(7-36)amide administration (Knapper *et al.* 1992). These mice have higher levels of adipose tissue LPL activity, which can be further stimulated by insulin, GIP and GLP-1(7-36)amide (Oben *et al.* 1992).

The evidence from human subjects is not as clear-cut. Some researchers have shown increased GIP secretion in obese subjects (Creutzfeldt *et al.* 1978; Willms *et al.* 1978; Jones *et al.* 1989), although not all authors agree (Service *et al.* 1984). One study has reported increased GLP-1(7-36)amide levels in obese diabetic subjects following an oral glucose tolerance test (Fukase *et al.* 1993), but in a recent study that we carried out in normal subjects we found diminished GLP-1(7-36)amide levels following a carbohydrate meal (Beety *et al.* 1994). It has been shown that the insulin stimulating action of GIP is reduced in diabetic subjects while that of GLP-1(7-36)amide and GLP-1(7-37) is preserved (Nauck *et al.* 1993a,b; Elahi *et al.* 1994).

Coronary heart disease

There is evidence that GIP stimulation of LPL can influence the extent and duration of postprandial lipaemia (Murphy *et al.* 1995). Studies in patients with coronary heart disease have demonstrated that these patients have an exaggerated postprandial triacylglycerol response to a test meal when compared with age-matched control subjects (Groot *et al.* 1991). It is believed that this increased plasma level of triacylglycerol could be atherogenic. It may be directly atherogenic through the generation of chylomicron remnants, circulating lipoprotein particles which can be taken up by macrophages leading to the formation of foam cells (Goldstein *et al.* 1980). Alternatively, it may be indirectly atherogenic via the influence of triacylglycerol-rich lipoproteins on the composition of other lipoprotein classes (Karpe *et al.* 1993).

As previously discussed, GIP is secreted in response to intestinal handling of fatty acids that require chylomicron transportation and can, like insulin, directly stimulate LPL, the activity of which is an important determinant of the extent and duration of postprandial lipaemia. Measurement of plasma insulin and GIP postprandially, therefore, can indicate absorption of nutrients and the potential for altered clearance of fat into adipose tissue. We have shown that Greek men have higher GIP levels in their plasma and in response to a mixed-nutrient test meal they reach peak plasma triacylglycerol levels faster than UK men (Knapper *et al.* 1995a). This is one aspect of our current investigations in both normal men and those at increased risk from coronary heart disease.

SUMMARY AND FUTURE DIRECTIONS

GIP and GLP-1(7-36)amide are both important endocrine components of the EIA. However, both hormones have a greater influence on the metabolism and subsequent fate of nutrients than simply through their actions on the endocrine pancreas. They offer a pathway by which dietary fat intake can be linked to adiposity, the further elucidation

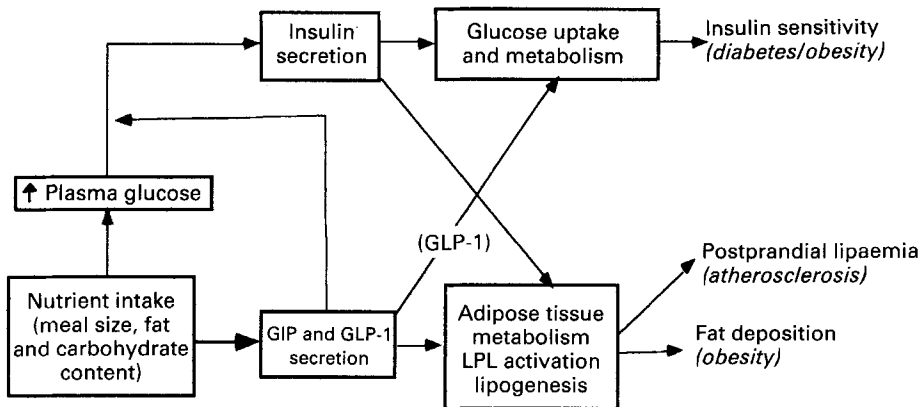


Fig. 4. Effects of nutrient and hormone interactions on metabolic events outside the gut. GIP, glucose-dependent insulinotropic hormone; GLP-1, glucagon-like peptide-I; LPL, lipoprotein lipase (EC 3.1.1.34).

of which is important to gain insight into the physiological control of fat deposition, and also the pathological condition of obesity and disease states such as coronary heart disease.

The diffuse location of receptors for both GIP and GLP-1(7-36)amide indicates the possibilities for other physiological roles in metabolism and serves to highlight the limitations of our current knowledge. The known and potential spectrum of interactions of these hormones with nutrients, hormones and enzymes external to the gut is summarized in Fig. 4.

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