Introduction
The gastrointestinal hormone GIP was initially isolated in 1969 from a crude porcine cholecystokinin extract as the contaminant responsible for the preparation’s apparent ability to inhibit gastric acid secretion [1]. It was named gastric inhibitory polypeptide on the basis of this biological activity. However, soon after its isolation another biological activity excited greater interest, namely its ability to act as a potent insulin secretagogue [2]. In the 1960s a series of classical studies had demonstrated that the insulin response to oral glucose was up to 50% greater than that observed after an intravenous glucose infusion producing similar circulating glucose levels [3]. The term entero-insular axis was coined by Unger and Eisentraut in 1969 [4] to embrace all those factors that contribute to enhancing insulin secretion after the ingestion of a meal and these putative gut factors were termed ‘incretins’. Numerous studies demonstrated that GIP played a major role as an incretin in the stimulation of insulin via the entero-insular axis [5] and the peptide was renamed glucose-dependent insulinotropic polypeptide, retaining the acronym GIP, to reflect a biological role that was perceived to be more physiologically relevant.

GIP alone does not, however, account for the full ‘incretin effect’ of the entero-insular axis. Immunoneutralization studies [6] and evidence from patients who had undergone intestinal resection have demonstrated that other factors are also involved. The isolation of glucagon-like peptide-1-(7-37)/(7-36)-peptide amide (GLP-1) in the 1980s was shortly followed by studies showing that it too must be considered as an incretin hormone with powerful insulinotropic effects [7]. From this time the role of GIP in the entero-insular axis has been closely bound up with GLP-1. Immunoneutralization and receptor antagonist studies have shown that GIP and GLP-1 together are sufficient to explain the full incretin effect, especially as both incretins may additionally interact with each other [8]. Investigation of the physiology and putative pathology of GIP subsequently focused on the dietary manipulation of its secretion and consequent effect on insulin secretion.

However, evidence is accumulating that GIP exerts biological effects outside the gut which can affect the metabolism and fate of absorbed nutrients. In particular, GIP has more recently gained recognition for its role in lipid metabolism. In man, fat is a more potent secretagogue of GIP than is carbohydrate [9], and the 24 h pattern of circulating GIP in subjects eating a typical Western diet closely parallels that of plasma triacylglycerol [10]. A putative role for GIP in dietary triacylglycerol disposal and adipose-tissue fat deposition opens up further areas of action for the hormone with a variety of both physiological and pathological implications. The following reviews the role of GIP in the stimulation of insulin secretion, with particular reference to its relationship to GLP-1, together with the extrapancreatic actions of GIP and their biological relevance.

GIP and the entero-insular axis
Both GIP and GLP-1 have insulinotropic actions on pancreatic B-cells in the presence of hyperglycaemia, stimulating insulin secretion and enhancing proinsulin gene expression [11]. Secreted in response to carbohydrate ingestion, they augment insulin secretion against the ‘set’ determined by circulating glucose concentrations. Receptors for both hormones have been found in rat and human insulinoma tissue, and rat islets and their receptor cDNAs have recently been cloned [12]. There is evidence that both receptors are functionally coupled to the adenylate cyclase system. Receptor activation additionally increases the intracellular Ca^{2+} concentration, possibly by activating a cell-surface cation channel [12]. Ca^{2+} influx is an essential part of the mechanism of GIP-stimulated insulin secretion, and B-cell glucose metabolism also appears to be a prerequisite for GIP-stimulated insulin secretion to occur [13]. Pre-exposure of B-cells to either GIP or GLP-1 has a ‘priming’ effect on insulin secretion.
enhancing the insulin-secretory response during a subsequent stimulation with glucose or other insulin secretagogues [14]. Whilst the actions of GIP and GLP-1 on the B-cell are very similar, their actions on other islet cells differ. GIP does not influence pancreatic A-cells under physiological conditions in man, but has been shown to stimulate D-cell somatostatin secretion in the perfused rat pancreas [15]. In contrast, GLP-1 at physiological levels inhibits glucagon secretion in various species, and is a potent simulator of somatostatin. It has been suggested that the effect of GLP-1 on insulin and somatostatin secretion is a direct one, while the effect on glucagon-secreting cells may be indirect, mediated by the paracrine effect of somatostatin [16].

GIP secretion is stimulated by actively transported carbohydrates and is dependent on the absorption of nutrients rather than their mere presence in the gut lumen [17]. Recent studies analysing the release of GIP from cultured endocrine cells have shown that GIP-secreting cells are responsive to adenylate cyclase activation and intracellular Ca\(^{2+}\) enhancement. Both depolarization by K\(^+\) and nutrient stimulation with glucose stimulates GIP release [18]. The mechanisms controlling carbohydrate-stimulated GLP-1 secretion are less well understood. GLP-1 is promptly released into the circulation after a meal, even though it is located in the distal small intestine. It is therefore likely that GLP-1 release is triggered by nervous reflexes in addition to nutrient stimuli acting at the luminal surface of the gut [19]. There is evidence in rats that GIP itself might act as a GLP-1 secretagogue [20], but, in contrast, human studies have shown that infusion of exogenous GIP does not stimulate GLP-1 secretion [21].

An intact N-terminal portion of both the GIP and GLP-1 molecule is necessary in order to preserve their insulinotropic activity [22,23]. Circulating levels of GIP after nutrient ingestion are some 4–5-fold higher than GLP-1, although in molar terms, GLP-1 has been shown to be a more potent insulin secretagogue than GIP [24]. However, the relative contributions of GIP and GLP-1 to the entero-insular axis are currently undergoing re-evaluation, as it has been recently shown that the proteolytic enzyme dipeptidylpeptidase IV initiates the rapid metabolism of GIP and GLP-1 in vivo. This enzyme inactivates GIP and GLP-1; the inactive fragments are, however, still detected in many radioimmunoassays. The additive insulinotropic effects of GIP and GLP-1 both in vivo in the perfused pancreas and in vivo when exogenous GIP and GLP-1 are infused in man are, however, sufficient to account for the full incretin effect [8], although it cannot at present entirely be excluded that other still unknown hormones are involved in the entero-insular axis.

The extrapancreatic effects of GIP
There is increasing evidence that GIP plays a metabolic role outside the gut. Specific GIP receptors have been found in a wide variety of tissues by both ligand-binding techniques and, after the cloning of the GIP receptor, detection of receptor mRNA [25] (Table 1). Although the hormone was initially named gastric inhibitory polypeptide after the biological action by which it was isolated, it inhibits gastric acid secretion in man only at supraphysiological levels [26]. Its effects on gastrin secretion remain to be clarified. GIP reduces glucagon-stimulated hepatic glucose production, although its mechanism of action may be an indirect one, since investigators have failed to find any evidence of GIP receptors in liver. Whilst GIP has traditionally been considered to be an endocrine hormone, GIP receptor mRNA has recently been found in several regions of the brain, suggesting a possible neurotransmitter role for GIP. However, the peptide ligand mRNA cannot be detected in brain by in situ hybridization techniques or PCR, suggesting that a novel GIP-like peptide might be present there [25].

In man, fat ingestion is a more potent stimulator of GIP secretion than is carbohydrate ingestion [9]. Increasing the fat content of the diet has been shown to increase both intestinal GIP content and mRNA, and GIP secretion [27,28]. The 24 h secretory pattern of GIP in volunteers eating a typical Western diet is far more prolonged than that of insulin, and closely parallels that of triacylglycerol [10]. These findings are consistent with the hypothesis that GIP plays a role in lipid metabolism. Both GIP and GLP-1 receptors have been detected in adipose tissue [25,29] and both hormones demonstrate direct anabolic actions on this tissue.

GIP has been shown to affect the insulin sensitivity of adipocytes. Incubation of isolated adipocytes with GIP increases receptor affinity and insulin-stimulated glucose transport [30]. GIP is also capable of stimulating glucose trans-
Table I
Detection of GIP and GLP-1 receptors in extrapancreatic tissues

<table>
<thead>
<tr>
<th>Tissue</th>
<th>GIP Receptor Specific hormone binding</th>
<th>GLP-1 Receptor Specific hormone binding</th>
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<tbody>
<tr>
<td>Liver</td>
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<td>?</td>
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<tr>
<td>Skeletal muscle</td>
<td>×</td>
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<tr>
<td>Adipose tissue</td>
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<td>Heart</td>
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<td>Lung</td>
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<td>Adrenal cortex</td>
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Port in isolated rat adipocytes and the incorporation of glucose into extractable lipids [31]. We have demonstrated that both GIP and GLP-1, in common with insulin but in contrast with GLP-2 and glucagon, stimulate fatty acid synthesis in explants of rat adipose tissue, as measured by the incorporation of \[^14C\]acetate into saponifiable fat [32]. GIP and GLP-1 may thus contribute in vivo to a more effective postprandial uptake of glucose and may enhance the effect of insulin on fatty acid synthesis from glucose as precursor. Consistent with this anabolic role, GIP has been shown to inhibit the lipolytic action of glucagon in adipocytes [33].

In man, the accumulation of adipose-tissue triacylglycerol from dietary fat is quantitatively more important than de novo lipogenesis. Adipose-tissue lipoprotein lipase (LPL) plays a key regulatory role in the hydrolysis of circulating triacylglycerol, liberating non-esterified fatty acids for uptake and storage within the adipocyte. In animal studies, exogenous GIP infusion has been shown to lower postprandial circulating triacylglycerol levels [34]. GIP has also been shown to stimulate the synthesis and release of LPL in cultured mouse preadipocytes [35]. We have demonstrated that GIP, in common with insulin, stimulates LPL activity in explants of rat adipose tissue, although GLP-1, over the same concentration range, is without effect [36]. In rats a high-fat diet increases GIP and insulin secretion, and elevates both basal and insulin- and GIP-stimulated LPL activity compared with control animals [37]. Under conditions of high fat and energy feeding, higher circulating levels of GIP and insulin together with an enhanced sensitivity of LPL to these hormones may therefore facilitate the uptake of circulating triacylglycerol and contribute to increased adiposity in some circumstances.

GIP – the link between diet and nutrient metabolism
The role of GIP in stimulating insulin secretion via the entero-insular axis is well established [38]; the physiological relevance of the extrapancreatic effects of GIP are, however, less well understood. GIP secretion is very sensitive to both acute and chronic changes of diet, in particular, changes in the dietary fat content. The degree to which fat stimulates GIP secretion is also species-dependent. In man, who normally consumes a relatively high-fat diet (a typical Western diet provides some 40% energy as fat), it is a more potent GIP stimulator than carbohydrate, whereas in rats and pigs, species whose diets usually provide <10% energy as fat, carbohydrate is a more potent GIP stimulator than fat [27]. The type of dietary fat consumed may also
influence GIP secretion in man; in a recent study we found that Greek subjects, who had similar total fat intakes to those in the U.K., but who had significantly greater intakes of mono-unsaturated fatty acids and lower intakes of saturated fatty acids, exhibited higher fasting and postprandial GIP levels than their U.K. counterparts [39]. The postprandial elevation of circulating GIP is dependent upon the size of the meal; this is true for both the carbohydrate and the fat component of the meal [40,41]. The contribution of the entero-insular axis is therefore proportionately greater after a large carbohydrate meal than a small one [40]. We have shown progressive parallel increases in post-heparin plasma LPL (LPL derived mainly from adipose tissue) and plasma GIP in vivo, after a series of meals whose fat content was increased from 20 to 80 g [41]. Insulin levels were unaffected by the fat content of these meals. The postprandial lipaemic responses to these meals of increasing fat content could therefore be moderated by stepwise increases in LPL activity, which in turn is mediated by fat-stimulated GIP secretion. This effect may be augmented by the action of insulin, but is not dependent upon a graded insulin response to increasing fat loads. GIP may therefore be the major hormonal signal linking meal size to postprandial lipase activity in the physiological control of lipaemia.

The period of growth from parturition to weaning is a time of rapid fat deposition in many species. An adequate reserve of adipose tissue may therefore be crucial to ensure the health and survival of the young animal, for example during the period of low food intake immediately after weaning. The suckling diet is high fat/low carbohydrate in most species. LPL activity is high during suckling and incorporation of dietary fatty acids is therefore an important pathway for adipose-tissue fat accretion during the suckling period. Studies with suckling pigs have demonstrated high circulating and intestinal GIP levels during the suckling period, which fell upon weaning [27]. It is possible that GIP is a major hormonal signal generated by milk consumption, activating LPL to aid the adipose-tissue deposition of dietary fat. The weaned pig, in contrast, consumes a carbohydrate-rich diet and deposits fat mainly through de novo lipogenesis. Manipulation of litter size in rats can lead to over- or under-nutrition during the suckling period, with consequent alteration of body-weight curves. This is due to differences in the degree of adiposity achieved by offspring rather than changes in their rate of growth. We have observed parallel changes in intestinal and circulating GIP levels during this period [42], giving additional evidence for a possible role for GIP in fat deposition during the suckling period and demonstrating the concurrent manipulation of both GIP concentrations and adiposity by dietary means.

A pathological role for GIP?

The observed biological actions of GIP at both pancreatic and adipose-tissue level make it an ideal candidate to be implicated in the pathology of obesity. There is considerable evidence linking an overactive entero-insular axis with the disordered insulin secretion and fat deposition observed in various obesity/diabetes syndromes in rodents [38]. Genetically obese ob/ob mice exhibit raised intestinal and circulating GIP, appear to be particularly sensitive to the insulino-notropic effect of gastrointestinal hormones and have raised adipose-tissue LPL levels [43]. Zucker fatty (fa/fa) rats have normal GIP responses to nutritional stimuli but show an increased sensitivity to the insulin-releasing action of GIP and GLP-1 [44]. The majority of human studies have, however, failed to find any differences in nutrient-induced GIP secretion between obese and normal-weight subjects, and it is therefore unlikely that GIP makes any major contribution to the hyperinsulinaemia or fat deposition of obesity unless obese subjects show an abnormal target cell sensitivity to GIP. There are conflicting reports of nutrient-induced GLP-1 secretion in obesity, with some authors reporting increased, and others diminished, secretion. Its role in obesity remains to be clarified.

Both GIP and GLP-1 have been implicated in non-insulin-dependent diabetes mellitus (NIDDM). Whilst circulating GIP levels are raised in some animal models of NIDDM, in man most studies emphasize that GIP levels are not elevated in diabetics [14]. Such differences that have been reported may be secondary to differences in gastric emptying and rates of nutrient absorption between diabetic and non-diabetic subjects. GLP-1 levels have been variously reported as raised or normal in NIDDM. mRNA levels for GIP and proglucagon are similar in diabetic and non-diabetic NOD mice, implying that insulin does not affect the gene expression of either hormone [45]. However, the overall
incretin effect is reduced in NIDDM and this has been attributed to a lack of sensitivity of the B-cell to GIP in these patients [46]. This lack of sensitivity can, however, be reversed pharmacologically; the sulphonylurea glyburide has been shown to enhance B-cell sensitivity to GIP in NIDDM, an action that contributes to its ability to improve glucose tolerance and insulin secretion in these patients [47]. GLP-1 is currently receiving much attention amongst diabetologists as a new tool for the treatment of diabetes. The combination of the 'glucagonostatic' action of GLP-1 [21] (see previous section) combined with its ability to increase glucose clearance [48] suggests that GLP-1 has a greater impact than GIP on glucose turnover in man; GLP-1 may therefore play a significant therapeutic role in the treatment of NIDDM.

GIP has been implicated in the disordered insulin secretion of a number of other diseases, including cirrhosis, chronic pancreatitis and Turner's syndrome. Aberrant adrenal sensitivity to GIP is also the cause of a rare form of corticotropin-independent Cushing's syndrome, in which food induces a GIP-mediated increase in plasma cortisol, leading to nodular adrenal hyperplasia [49]. Notably, a recent study has demonstrated increased GIP and insulin responses to a mixed meal in subjects with essential hypertension or a family history of hypertension, compared with normotensive controls [50]. The possibility that altered GIP secretion contributes to the pathogenesis of hyperinsulinaemia in essential hypertension is of potential importance, and warrants further investigation.

**Conclusions**

GIP makes a considerable contribution to insulin secretion in man via the entero-insular axis. Its secretion is closely controlled by the size and macronutrient content of a meal. The evidence that GIP also exerts insulin-like anabolic effects on adipose tissue underlines its importance in providing a mechanism whereby diet is linked to the metabolic fate or nutrients (Figure 1). This has a wide variety of implications both in man and in other mammalian species, ranging from the physiological control of fat deposition and nutrient partition during periods of high dietary intake (for example, in the young suckling animal), to a possible role in the aetiology and pathology of various disease states in man. Investigation of the actions of gastrointestinal hormones on metabolic events outside the gut is essential to our understanding of both physiological and pathological processes which are influenced by diet.


**Figure 1**

Interactions between diet, GIP secretion and metabolic events outside the gut.
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Regulatory peptides in the control of metabolism during starvation and exercise

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This paper will review the potential metabolic actions of regulatory peptides. The peripheral responses of regulatory peptides to exercise and starvation will be examined in normal, obese and diabetic subjects, and two groups of regulatory peptides will be examined: (1) those that are stimulated by food ingestion and play a role in the entero-insular axis, e.g. gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 (GLP-1); (2) those that are not or are minimally stimulated by food ingestion but are released after physiological events such as starvation and endurance exercise, e.g. secretin, glucagon and vasoactive intestinal polypeptide (VIP).

Starvation and endurance exercise

These two physiological states may be regarded as similar. Both initially rely on stored carbohydrate but eventually switch to gluconeogenesis and fatty acids for energy supplies. They both therefore represent states of negative energy balance. It may be hypothesized that the body's response to these two physiological events, including the hormonal response, may be similar.

Actions of regulatory peptides relative to negative energy balance

Classical studies by Cahill et al. [1] in human starvation suggested that insulin appeared to be dominant to other hormones in controlling fuel mobilization and metabolism during starvation, but other regulatory peptides also play a proven role or a putative role. Glucagon and VIP mobilize glucose from glycogen [2]. There is evidence in laboratory animals that VIP [3], secretin [4] and glucagon [5] stimulate lipolysis in vitro although the relevance of these findings to the human adipocyte is questioned [6,7]. GIP stimulates the incorporation of fatty acids into adipose tissue [8].

Starvation

In 1975 this group first showed that circulating levels of secretin rose in nine healthy subjects during a 72 h starvation period [9]. The levels achieved were several orders of magnitude higher than those recorded after intraduodenal acid. Further studies [10] suggested that during acute starvation a rise in triacylglycerol concentration results from the increased availability of free fatty acids, and that elevated secretin and glucagon levels enhance lipolysis and hence provide substrates for triacylglycerol synthesis. Further studies concentrated on the mechanism of hormone release and the possible biological effects. Henry et al. [11] showed that secretin levels elevated by starvation were rapidly suppressed on refeeding. Although secretin may play a role in lipolysis during starvation, Beringer et al. [12] were unable to stimulate the production of free fatty acids after infusions of secretin into human volunteers which resulted in secretin levels that mimicked those noted in starvation. Bell et al. [13] failed to suppress secretin levels after starvation by administering the H2-receptor antagonist drug, cimetidine. However, they suggested that this may be due to inadequate suppression of gastric acid output or to some alternative stimulus to secretin release during fasting. Shulkes et al. [14] examined the tissue content of hepatic glycogen.