**The influence of Glucose-dependent Insulinotropic Polypeptide (GIP) on human adipose tissue and fat metabolism: implications for obesity, type 2 diabetes and Non-Alcoholic Fatty Liver Disease (NAFLD)**

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**Abstract**

Glucose-dependent insulinotropic polypeptide (GIP) and glucagon like peptide (GLP-1) are the two incretin hormones secreted by the enteroendocrine system in response to nutrient ingestion. Compared with GLP-1, GIP is less well studied as a hormone or as a potential pharmacological treatment. Beyond its insulinotropic effects in the pancreas, GIP has important biological actions in many other tissues but its role in dietary fat metabolism and lipid storage in adipose tissue has been most studied. It is still unclear if such effects of GIP on adipose tissue/fat metabolism are protective or deleterious in the long term. Antagonising GIP actions through genetic and chemical disruption in mice models prevented diet induced obesity and improved insulin sensitivity. Whilst such effects of GIP antagonism are yet to be evaluated in humans, recent studies using combined GIP and GLP-1 agonists have shown weight reduction and improved glycaemic control in people with type 2 diabetes (T2D). Therapeutic manipulation of GIP physiology is intriguing in that both agonists and antagonists of GIP are being investigated to explore their potential weight-reducing and other metabolic benefits in people with obesity, T2D and non-alcoholic fatty liver disease (NAFLD).

This review will discuss the physiological effects of GIP on fat metabolism in human adipose and other non-adipose tissues such as liver, pancreas, skeletal muscle and heart, describe where the actions of GIP may contribute to the pathophysiology of obesity, T2D and NAFLD and finally describe the therapeutic implications of GIP antagonism and agonism in these conditions.

**Key Words**

Glucose dependent Insulinotropic Polypeptide, adipose tissue fat metabolism,

Non-esterified fatty acids (NEFA) Triacylglycerol (TAG), adipokines

Obesity, Type 2 diabetes, Non-alcoholic fatty liver disease (NAFLD)

**Introduction**

Glucose-dependent Insulinotropic Polypeptide (GIP) and the other incretin hormone glucagon like peptide-1 (GLP-1) are important gut peptides secreted by the enteroendocrine system in response to nutrient ingestion. While GLP-1 has been extensively investigated, and manipulation of its physiology forms the basis for the use of incretin-based glucose lowering and weight loss medications, the potential for GIP as a therapeutic option is less well studied. GIP exerts a variety of important physiological effects in multiple tissues evidenced by the widespread distribution of the human GIP receptor (GIPR). Besides its expression in the pancreas where it mediates its insulinotropic effects, the human GIPR is widely expressed in adipose tissue, gut, bone and trachea; it is also detected at lower levels in the brain, heart, spleen, thymus, blood cells, lung and kidneys [1-3]. Functional GIPR is present in human adipocytes, and its expression increases as the differentiating adipocytes progressively accumulate lipid droplets; GIP has been demonstrated to play a critical role in regulating fat metabolism and lipid storage [1, 4].

Results from several animal and human studies strongly support a physiological role for GIP in promoting lipid deposition in adipose tissue in response to nutritional excess [5]. Amongst the various nutrient stimuli, fat is the most potent macronutrient to stimulate GIP secretion in humans [6-8]. The diurnal variation of endogenous GIP concentrations in healthy humans parallels that of serum triglyceride concentrations suggesting an important modulating role in the post-prandial metabolism of fat [9]. In this review, we focus on the role of GIP in regulating human fat metabolism and review the evidence from animal models that laid the foundation for identifying the physiological effects of GIP in humans. We also consider the consequences of excess GIP secretion that may contribute to the pathophysiology of obesity, insulin resistance and NAFLD and discuss the therapeutic implications of manipulating this component of the incretin axis.

*The association between GIP, body fat distribution and insulin resistance*

GIP is proposed to influence fat deposition in adipose and non-adipose tissues and higher GIP secretion may modulate ectopic fat deposition promoting excessive visceral and liver fat accumulation [10]. A cross sectional study of 1400 Danish people suggested that higher serum fasting GIP concentrations were associated with an unhealthy body fat distribution, independent of plasma insulin concentration [11]. A genome wide association study (GWAS) including >120,000 people of European descent showed a strong association between body mass index and single nucleotide polymorphisms (SNPs) of the GIPR locus [12]. Similarly, SNPs of GIP were also linked to body fat distribution and increased visceral fat accumulation in two separate studies, involving approximately 3000 Japanese and Chinese people respectively [13, 14].

Subcutaneous and visceral fat are a major source of circulating non-esterified fatty acids (NEFA). Chronic elevations of NEFA interfere with insulin signalling, inhibit glucose uptake [15, 16] and result in lipid accumulation in adipose and non-adipose tissues such as liver, skeletal muscle and pancreas leading to insulin resistance and type 2 diabetes (T2D) [17]. The results of animal studies have suggested GIP/GIPR-mediated effects may link the consumption of a high-fat/energy dense diet with the development of obesity and insulin resistance [18, 19]. Genetic and chemical disruption of GIP signaling in mouse models of obesity-induced insulin resistance protects against the deleterious effects of high-fat feeding by preventing lipid deposition, adipocyte hypertrophy, reducing triacylglycerol (TAG) deposition in liver and skeletal muscle and maintaining insulin sensitivity [20, 21]. Whilst GIP antagonists could potentially offer a novel approach in the treatment of diet-induced obesity and T2D [22], dual GIP and GLP-1 agonists have shown promising results in improving glycaemic control and weight reduction in patients with T2D [23]. In view of both beneficial and undesirable effects, targeting GIP, either by blocking or enhancing its action, is likely to compromise other essential physiological functions making therapeutic manipulation problematic. An understanding of the physiology of GIP beyond its role in fat metabolism, in non-adipose tissues and other vital organs like brain and bone is critical.

**1. Normal post-prandial lipid metabolism**

Triacylglycerol (TAG), commonly referred to as triglyceride, is the major component of dietary fat whilst phospholipids and other sterols form a minor part. Dietary fat is emulsified by enzymatic breakdown in the gastrointestinal tract and TAGs are hydrolysed to non-esterified fatty acids (NEFAs) and glycerol. These hydrolysed molecules are absorbed across the intestinal walls, re-synthesised into TAGs and packaged into complex lipids such as lipoproteins and chylomicrons in the endoplasmic reticulum and secreted into the lymphatic system and circulation [24]. Whilst some of the lipid complexes reach skeletal muscle and are oxidised to meet energy requirements, the majority are stored in adipose tissue. Some remnant chylomicrons also reach the hepatic circulation to be taken up by the liver through receptor mediated endocytosis **(Figure 1).**

At adipose tissue endothelium, lipid complexes are hydrolysed into NEFAs by the enzyme lipoprotein lipase (LPL) and re-esterified into TAGs within adipocytes and stored in the form of lipid droplets, a process referred to as lipogenesis [25]. Insulin promotes this process by stimulating LPL activity and NEFA esterification [26, 27]. Excess carbohydrate is also converted to NEFAs by *de novo* lipogenesis (DNL).With a finite capacity of subcutaneous adipose tissue to expand, excess fat is deposited in visceral adipose tissue, which is capable of storing dietary fat more densely than subcutaneous adipose tissue [28, 29]. In healthy lean people visceral fat barely contributes to systemic NEFA concentrations but in contrast in people with visceral obesity, omental and mesenteric fat delivers excess NEFA into the systemic circulation and when supplies exceed the oxidative capacity, lipids accumulate in the non-adipose tissues including the liver, pancreas and skeletal muscle **(Figure 1)** [30].

During periods of energy restriction (starvation, post-exercise and physical stress), adipose tissue TAGs are hydrolysed in a step-wise manner to glycerol and NEFAs to meet energy requirements. This process is mediated by the enzymes adipose triglyceride lipase (ATGL) and hormone sensitive lipase (HSL) and inhibited by insulin [25, 31]. A balance between energy storage and breakdown usually exists during eucaloric states, but becomes dysregulated when energy intake exceeds requirements over time, with increased TAG storage leading to adiposity in the long term. This enzyme mediated process of lipid metabolism is regulated by hormones including insulin, catecholamines, growth hormone and glucocorticoids [25]. We now know that GIP also has a prominent role in various steps of lipid metabolism**.** In the following sections, we discuss the potential role of GIP in lipid metabolism in adipose and non-adipose tissues.

**2. The role of GIP in regulating lipid metabolism in adipose and non-adipose tissues**

Evidence from animal studies suggest GIP may have a similar regulatory role as insulin in the process of lipogenesis. GIP secreted after fat ingestion under normoglycaemic conditions is not insulinotropic. However, under normal physiological conditions where nutrient composition is a mixture of carbohydrate, fat and protein, secretion of GIP concomitantly with insulin makes it difficult to assess the independent actions of GIP. The effects of GIP on NEFA incorporation in rat epididymal fat pads was lower with GIP alone in the incubation medium compared to the combination with insulin, suggesting insulin may be necessary for GIP to exert its effects [32]. As a major physiological role of GIP is to enhance insulin secretion, it could be assumed that GIP merely enhances NEFA incorporation through hyperinsulinaemia and may not have a direct role. However, the experiments from Miyawaki et al. with leptin deficient obese mice (*Lepob/Lepob*) have disproved this concept. *Lepob/Lepob* mice develop marked obesity due to hyperphagia and have gross hyperinsulinaemia. Double homozygous *Lepob/Lepob and* GIP receptor knockout mice (Gipr–/–) were shown to have 23% reduced body weight compared to *Lepob/Lepob* alone. Both these groups had a similar level of hyperinsulinaemia, suggesting that GIP action is not solely mediated through insulin and it has direct influence on adipose tissue lipid deposition [20]. Most animal studies demonstrate that GIP has an important role, together with insulin, in regulating LPL and TAG clearance from the systemic circulation to promote NEFA incorporation into adipose tissue. Such metabolic properties of GIP in humans gained attention only recently. Studies investigating the effects of GIP on human adipose tissue are listed in **Table 1 and reviewed in detail in the following sections.** Theeffects of GIP on lipid metabolism and the potential underlying pathways in different tissues are shown in **Figure 2.**

**2.1 Effects of GIP on adipose tissue blood flow in humans**

Adipose tissue blood flow (ATBF) varies significantly during different physiological states (e.g. feeding, fasting and exercise). An increase in blood flow is an important marker of tissue metabolic activity [25]. Acute GIP infusions (infusion rate, 1.5 pmol/kg/min) under hyperinsulinaemic hyperglycaemic clamp conditions in healthy lean subjects increased ATBF significantly compared to placebo [33]. The insulin independent effects of GIP were difficult to tease out in this study, but similar experiments, using octreotide to inhibit insulin, showed these effects of GIP may be insulin independent [34]. The increase in ATBF by GIP was thought to be mediated by vasodilation and increased capillary microvascular blood volume [35]. Such effects of GIP on ATBF were not emulated in obese and impaired glucose tolerant subjects; however, when experiments were repeated after weight loss, these actions on ATBF were partly restored [36, 37]. These experiments indicate that GIP increases ATBF thereby providing more substrate (TAG) to adipose tissue resulting in increased TAG hydrolysis and esterification of NEFA in adipose tissue however, these effects of GIP appear to differ with obesity and glycaemic states.

**2.2 Effects of GIP on NEFA metabolism in human adipose tissue**

GIP promotes NEFA esterification and storage of TAG in adipose tissue. The effects of acute GIP infusion on plasma concentrations of NEFAs in healthy males were studied by infusing 20% intra-lipid (a chylomicron like emulsion) with or without glucose infusions [38]. In this study, GIP with co-infusion of intra-lipid and glucose caused greater reductions in NEFA concentrations compared to GIP with intra-lipid alone thereby indicating insulin secretion (as a result of glucose infusion) to be an important factor in lowering NEFAs. In healthy lean subjects, acute GIP infusions (1.5 pmol/kg/min) under hyperinsulinaemic hyperglycaemic clamp conditions increased TAG hydrolysis, glucose uptake and reduced NEFA output compared to placebo [33]. Another study showed similar effects on NEFA reductions with acute GIP administration (2pmol/kg/min) in healthy obese men in a euglycaemic fasting state [39]. With the effects of GIP on re-esterification of dietary fat, plasma TAG would be expected to reduce in the post prandial state but surprisingly there was no such reduction with GIP infusions in studies using meal experiments [38, 40]. GIP-mediated effects on lipid metabolism via peripheral lipid clearance in humans warrants further examination.

We studied the effects of GIP infusions (2pmol/kg/min) for 4 hours under hyperglycaemic clamp (8mmol/l) in people categorised into four groups based on their weight and glucose tolerance [lean, obese, obese with impaired glucose regulation (IGR) and obese with T2D] [41]. In the first 3 groups GIP increased insulin secretion compared to placebo. Plasma NEFA reduced in all the experiments but there was no significant difference between GIP or placebo infusions indicating the effects of GIP were overridden by co-secreted insulin under hyperglycaemic clamp conditions. However, in the obese T2D group, although the insulin secretion was diminished with GIP, NEFA concentrations were significantly lower with GIP infusion compared to placebo demonstrating an insulin independent effect of GIP on NEFA metabolism. Additionally, GIP increased TAG content in the subcutaneous adipose tissue in participants who were obese with T2D but not in those without diabetes despite greater insulinotropic activity. Thus, in people with T2D, where GIP has a blunted insulinotropic activity in pancreatic β-cells, there appears to be a dissociation of the effects on adipocytes with preserved lipogenic actions.

**2.3 The effects of GIP on lipid metabolism enzymes**

Cultured pre-adipocytes incubated with GIP showed enhanced LPL activity and increased clearance of triglyceride rich proteins and chylomicrons from the circulation assisting in lipid storage, an action similar to insulin [20, 42]. Furthermore, GIP was shown to have a direct influence on LPL activity in explants of rat epididymal adipose tissue. When GIP was combined with insulin, the LPL activity was significantly greater than either hormone alone suggesting GIP complements insulin in enhancing triacylglycerol clearance. Such effects were not observed with the other incretin hormone, glucagon like peptide-1 (GLP-1) [43]. The pathways through which GIP stimulates LPL involves many serine/threonine protein kinases. GIP increases phosphorylation of protein kinase B (PKB) and decreases the phosphorylation of LKB1 and AMP-activated protein kinase (AMPK) that leads to activation of LPL and triacylglycerol accumulation in the adipocytes [44]. The lipogenic effect of GIP, in the presence of insulin was shown to be partially mediated by up-regulation of adipocyte *LPL* gene transcription [45]. In addition to lipogenic effects, GIP may increase lipolysis along with induction of inflammatory adipokines [46-48]. Lipolytic effects of GIP may be enhanced with insulin deficiency [49]. GIP induced lipolysis was shown to be through phosphorylation of HSL, a process inhibited in the presence of insulin [47]. The effects of GIP on lipolytic enzymes (HSL and ATGL) is less extensively studied.

Very few studies have evaluated the *in-vivo* effects of GIP on lipid metabolism enzymes in humans **(Table 1).** The effects of postprandial insulin and incretin hormones on LPL activity were studied in lean and obese women using carbohydrate meal alone or combined with intravenous infusion of octreotide to suppress insulin. LPL activity was unchanged in both experiments and was unaffected by octreotide infusion, indicating LPL activity is not obliterated by inhibiting insulin [50]. In healthy obese men, acute GIP administration (2pmol/kg/min) in euglycaemic fasting state reduced mRNA expression and enzyme activity of 11β hydroxysteroid dehydrogenase type-1(11β HSD-1), an enzyme that converts inactive cortisone to active cortisone [39]. Authors from this study speculated that GIP-induced effects on lipid metabolism are due to the alteration in active cortisol content within adipose tissue. *In-vitro* experiments by the same group using 3T3-L1 differentiated cells showed that GIP reduced activity and expression of 11*β*- HSD1 and lowered the expression of ATGL and HSL. We measured mRNA expression of LPL, ATGL, and HSL in subcutaneous adipose tissue to determine the molecular mechanisms that might account for changes in NEFA and TAG content after GIP infusions in our study [41]. Surprisingly, we observed no significant changes in enzyme expression. This may represent a time course phenomenon with changes in gene expression with GIP in human adipose tissue occurring over a longer interval.

**2.4 The effects of GIP in adipose tissue inflammation**

Adipose tissue is an endocrine organ that secretes several adipokines (for example leptin and adiponectin) and pro-inflammatory cytokines (for example TNF-α and IL-6) that may modify insulin resistance. Prolonged exposure to these inflammatory agents and excess NEFAs from visceral and ectopic fat interferes with insulin signalling in skeletal muscle and liver leading to insulin resistance [17]. Direct effects of GIP on leptin expression were not evaluated but adiponectin levels may be reduced by GIP, as suggested in studies of GIPR knock out mice [51]. TNFα is a pro-inflammatory adipokine present in high levels in obesity and insulin resistant states. Interleukin 6 (IL-6) expressed in multiple tissues worsens insulin resistance in adipose tissue and liver while improving insulin sensitivity in muscle. A previous study from our group showed that acute GIP infusions in obese individuals with T2D did not alter circulating adipokine levels, but acute infusion of GLP-1 suppressed IL-6 [52]. An in-vitro study of human subcutaneous pre-adipocytes showed that GIP induced mRNA expression of pro inflammatory IL-6 and IL-1β but not TNFα. Inflammatory adipokine induction by GIP involves pathways similar to those inducing lipolysis by activating HSL [47].

Monocyte Chemoattractant Protein-1 (MCP-1) is a key regulator chemokine involved in migration and infiltration of monocytes and macrophages and has a role in the aetiologies of obesity and diabetes-related diseases [53]. Intraperitoneal injections of GIP in mice increased MCP-1 and IL-6 expression in adipose tissue [54]. A study in humans showed increased MCP-1 and MCP-2 expression with GIP infusions [55]. Osteopontin is another important pro-inflammatory cytokine expressed in adipocytes and other cells like osteoclasts, smooth muscle cells and hepatocytes which increases macrophage accumulation and inflammation that leads to insulin resistance [56]. GIP was shown to enhance osteopontin expression in primary rodent adipocytes [57]. Experiments on human adipocytes expressing a genetic variant of GIPR with diminished function, showed reduced OPN levels and improved insulin sensitivity [58]. There is emerging evidence from animal studies that GIP enhances pro-inflammatory adipokines but there is little evidence in humans which requires further exploration.

* 1. **GIP and liver fat accumulation**

*Normal liver metabolism* The liver processes large amount of NEFA but stores only a small amount of lipid in the form of TAGs in healthy individuals. Most NEFA in the liver are oxidized by mitochondrial β-oxidation to generate ATP and ketone bodies, while some are esterified to glycerol-3-phosphate and cholesterol within the hepatocytes to generate TAG or cholesteryl esters respectively. These complex lipids are either stored in cytoplasmic lipid droplets or secreted into bloodstream as very low density lipoproteins (VLDL) [59] which when released into the blood stream are oxidized in skeletal muscle or stored in adipose tissue as TAGs [60] (**Figure 1**). Liver also has the ability to convert glucose into NEFA when faced with excess carbohydrate, a process known as *de novo* lipogenesis (DNL). This pathway is under-utilised in normal healthy conditions, but in metabolic states of insulin resistance and T2D, DNL is increased. In combination there is a reduction in mitochondrial β-oxidation of NEFA leading to excess intra-hepatic TAG. The consequences of this include storage in the liver (hepatic steatosis) or export from the liver as VLDL, giving rise to the typical dyslipidaemia [59].

The presence of GIP receptors in liver is controversial. Studies in animal models suggest GIP enhances lipid deposition in liver and inhibition of GIP signal by genetic manipulation prevents this process [20, 61-63]. Mice with adipose tissue specific GIP receptor knockout (GIPR -/-) had lower TAG content and hepatic steatosis on high fat feed. Expression of the inflammatory adipokine, IL-6, mediated by suppressor of inflammatory cytokine signaling (SOCS3) was significantly reduced in GIPR -- mice suggesting GIP may mediate inflammatory change within a fatty liver [64]. In humans, increased post-prandial release of GIP has also been implicated in the pathophysiology of NAFLD: patients with NASH exhibit a prolonged GIP elevation after ingestion of a high fat load, compared with age, body mass index, and sex-matched healthy controls. The GIP response correlated directly with the degree of hepatic steatosis [10].

There is some evidence that GIP release is implicated in mediating excessive liver fat accumulation with consumption of high glycaemic index (GI) foods. Comparison of the effects of simple sugars (e.g. sucrose) vs. complex sugars (e.g. isomaltulose) demonstrate contrasting intestinal hormonal responses. More rapid digestion of sucrose and more proximal small intestinal glucose uptake stimulates K cells to release GIP; more slowly digested isomaltulose, bypasses K cells (with minimal GIP release) but stimulates GLP1 release by distal small intestinal L cells [65]. In humans, delaying glucose absorption and thus reducing GIP release, with acarbose, an α-glucosidase inhibitor, is associated with a reduction in hepatic fat content [66]. In mouse models, chronic diets enriched with sucrose, but not isomaltulose, is associated with fatty liver; sucrose intake resulted in higher glucose absorption and post-prandial GIP levels. However, no difference in hepatic fat accumulation was observed between the diets enriched with sucrose or isomaltulose when fed to mice with deletion of GIP receptors (GIPR−/− mice), suggesting that GIP release/signalling mediates the development of fatty liver in response to different dietary sugar consumption [67].

* 1. **GIP and lipid metabolism in other non-adipose tissues**

*Pancreas* Prolonged exposure of the pancreatic islets to excess NEFA causes lipotoxicity that interferes with insulin signalling, glucose uptake and glycogen synthesis and leads to beta cell dysfunction [15, 16]. People with obesity, fatty liver, T2D and excess visceral fat content all have higher intra-pancreatic fat [68-70]. Although increased pancreatic lipid is associated with metabolic dysfunction, there is no evidence to suggest that inert fat storage has direct lipotoxic effects on pancreas [68, 71].

*Skeletal muscle* NEFA uptake in the skeletal muscle occurs when substrate availability exceeds the energy expenditure for metabolic demands. Once taken up in the skeletal muscle NEFA are either oxidised or synthesised to TAGs and stored as intramyocellular lipid (IMCL) [72]. Studies suggest that insulin resistance in skeletal muscle is a consequence of deleterious lipid intermediates such as diacylglycerols and ceramides but not necessarily due to IMCL content [73]. IMCL may therefore act as an energy reservoir for increased demands during exercise and the harmful effects may not occur with normal oxidative capacity in skeletal muscle [74].

*Role of GIP* So far there is no clear evidence on GIP having direct effects on lipid accumulation in pancreas and skeletal muscle but it may influence these processes indirectly by excess TAG accumulation in subcutaneous and visceral adipose tissue which in turn leads to lipid accumulation in these non-adipose tissues (**Figure 2**).

*Cardiac muscle* GIP signalling may regulate TAG metabolism in cardiomyocytes with GIP receptors present in animal and human myocardial tissues. Although these effects in humans are yet unknown, a recent study in mice showed that GIPR activation through a GIP agonist increased myocardial fatty acid oxidation and such effects were abolished by GIP antagonists [75]. In the same study, GIP receptor knockout mice (Gipr –/–) had increased myocardial TAG content a suggesting GIP may increase lipid oxidation in the cardiomyocytes. Furthermore, both Gipr –/– mice and cardiomyocyte selective Gipr –/– mice showed enhanced survival and reduced adverse effects on the left ventricle after myocardial infarction. Myocardial TAG was also increased in these Gipr –/– mice along with reduced expression of the lipolytic enzyme HSL suggesting GIP induces lipid oxidation in the myocardium mediated through activation of HSL [75]. These results indicate blocking GIP signal has cardioprotective effects in mice after myocardial infarction through reduction in lipid oxidation in the myocardium.

1. **The therapeutic potential of GIP**

Several GLP-1 agonists including longer acting agents are currently being used in the treatment of T2D and obesity [76]. In contrast, GIP cannot be used as a glucose lowering therapy on its own due to diminished insulinotropic activity in T2D [77, 78]. Activation of the GIP receptor (GIPR) is somehow glucose dependent, with GIPR expression down regulated in response to hyperglycaemia [79]. This blunted effect of GIP was shown to reverse with normalisation of glucose in people with T2D after intense insulin treatment and also with other oral hypoglycaemic agents [80, 81]. GIP also increases glucagon secretion; while this effect appears to be protective in healthy people during fasting conditions [82, 83], it may worsen glucose intolerance in T2D [84, 85].

Studying the metabolic effects through GIP signal blockade helps to understand the overall contribution of GIP in glucose regulation, adiposity and insulin resistance. Most studies in GIPR knockout mice showed improved glucose tolerance and insulin sensitivity on high fat diet in contrast to what would have been expected with the loss of insulinotropic activity from GIP [20, 86-88]. GIPR antagonists and active immunisation of GIP in animals on high-fat diets, show reduced body weight, enhanced loco-motor activity, improved HbA1c, glucose tolerance and insulin sensitivity [21, 61, 62]. As the metabolic profile improves with inhibition of the GIP signal, it is possible that the negative effects of GIP inhibition in the pancreas are compensated by weight loss and beneficial effects in other tissues, indirectly leading to improved beta cell function and insulin sensitivity.

* 1. **The effects of GIP antagonists**

The evidence on the effects of GIP antagonists in humans has only just started to emerge. GIP(3-30)NH2, a competitive antagonist of the human GIP receptor, blocks GIP mediated G protein signalling and release of pancreatic hormones [89, 90].

A randomised, placebo controlled study in lean, young males showed that acute infusions of the antagonist, GIP(3-30)NH2 for 45 minutes attenuated GIP induced insulin secretion under hyperglycaemic clamp conditions [91]. Although the experiments in this study were not primarily designed to evaluate lipid metabolism, there were no significant changes observed in plasma NEFA, TAG and cholesterol during this study. In another study, acute infusions of the antagonist, GIP (3-30)NH2 not only reduced the incretin effect but also eliminated the previously observed GIP augmented increase in ATBF and TAG uptake into adipose tissue in healthy males. [92]. The effects of longer term GIP antagonism in humans has not been studied and evaluating such effects on adipose tissue metabolism, insulin resistance and changes in weight is warranted.

* 1. **GIP agonists in T2D**

In contrast to GLP-1, treatment with GIP alone has no additional glucose lowering benefits and does not result in weight loss in T2D. Surprisingly, when GIP was combined with GLP-1 and glucagon, glycaemic control improved along with weight reduction and reversal of steatohepatitis in diet induced obese mice [93, 94]. The longer term effects of selective GIP agonists have not been evaluated in humans but a dual GIP/GLP-1 agonist (RG7697) showed reductions in fasting and post prandial glucose levels people with T2D [95]. Similarly, treatment with another dual GIP/GLP-1 receptor agonist (NNC0090-2746) in patients with suboptimal control of T2D for 12 weeks showed reductions in HbA1c, cholesterol and body weight compared to placebo [96]. Interestingly patients starting with a lower HbA1c (< 8.5%) had greater weight loss in this study. LY3298176 (tirzepatide) is the latest dual GIP/GLP-1 agonist intended for human use as a weekly subcutaneous injection [97]. A randomised phase 2 study involving over 300 people with T2D, comparing the effects LY3298176 with a long acting GLP-1 agonist (dulaglutide) and placebo for 26 weeks showed better glucose control and greater weight loss with LY3298176 [23].

Whilst the majority of evidence from animal studies pointed towards diet-induced weight gain with GIP, achieving significant weight loss when combined with GLP-1 in human studies is a paradoxical and interesting finding. GIP responsiveness improves with reversal of hyperglycaemia and it is possible the effects of GIP are enhanced with improved glycaemic control, as seen with the post hoc analysis of the study using dual agonist NNC0090-2746 [96]. In contrast to the effects of GIP on glucagon secretion, the dual agonist (LY3298176) reduced fasting plasma glucagon which may partly contribute to improved glycaemic control [23]. Although these effects may explain the improved insulinotropic activity, they do not explain the weight reduction, which may be mediated mainly by the GLP-1 agonist activity of the drug. Perhaps, the effects of chronic administration of GIP are different to those seen with acute infusions. It is also possible that GIPR may be down regulated with longer term agonist treatment resulting in the effects expected from an antagonist [98]. Although the dual agonists have more affinity to GIPR, the possibility of exaggerated GLP-1 activation with these agents cannot be completely excluded.

Studies in mice demonstrated metabolic benefits of dual agonist by reduction in energy intake and therefore reduced body weight [99-101] but evidence for such effects of GIP is lacking in humans [102]. GLP-1 infusions have shown reduced energy intake, but a co-infusion of GIP with GLP-1 caused increased energy intake with no appetite reducing effects [103]. It is also possible the effects of longer term GIP treatment are centrally mediated. Recent data from transgenic mice with manipulated GIPR cells in the brain showed that direct activation of hypothalamic GIPR cells reduced food intake [104]. As both GIPR and GLP-1 receptors are expressed in the hypothalamus in humans, it is possible that activation by dual agonists may have synergistic effects on energy balance and weight reduction. The effects of GIP agonists and antagonists on fat metabolism have not been studied and evaluating these aspects during longer duration treatment with these agents is warranted.

* 1. **The effects of GIP on fat metabolism: Protective or detrimental?**

Storage of energy deposits in adipose tissue is an adaptive mechanism of evolutionary importance. The excess fat deposition by GIP seen in animal studies was only seen with high fat diets and not observed with normal diet. Perhaps the effect of GIP in adipose tissue was a protective mechanism during the times of under-nutrition and famine which may have become maladaptive with surplus energy intake. Whilst clearance of NEFA from circulation by GIP is protective in reducing lipotoxicity, unhealthy distribution of fat and visceral adiposity potentially mediated by GIP would have long term deleterious effects. GIP also has lipolytic properties and may increase pro-inflammatory adipokines. It can be speculated that with consumption of energy dense high fat diet, the effects of GIP may lead to a vicious cycle of fat storage in adipose and non-adipose tissues and lipolysis from surplus lipid storage releasing excess NEFA which further exacerbates insulin resistance and obesity.

The physiological role of GIP in adipose tissue in T2D is not fully understood. Energy dense, high fat diets in obese individuals with T2D could result in exaggeratedfat storage (through exaggerated GIP release) even in the absence of adequate insulin secretion. In healthy individuals, where adipose tissue insulin sensitivity is preserved, insulin lowers NEFAs postprandially and suppresses lipolysis independently, suggesting that the effects of GIP are trivial under these conditions. However, in T2D where insulin secretion is impaired and adipose tissue is insulin resistant, the effect of GIP may assume greater importance, promoting lipid accumulation in adipocytes. This is consistent with animal data where GIP did not promote fat accumulation in adipocytes with normal insulin sensitivity, with (GIPR-/-) mice showing similar adiposity to wild-type on a control diet [20]. However, under the conditions of diminished insulin action, GIP was shown to promote subcutaneous and visceral adipose tissue expansion and decreased fat oxidation [105].

**Conclusion**

GIP appears to be a multi-dimensional hormone with both beneficial and potentially deleterious effects in many tissues. GIP has a definitive role in fat metabolism in humans with the most convincing evidence being its ability to enhance NEFA incorporation into adipose tissue with consistent reductions in plasma NEFA after GIP infusions. The effects of GIP on enhancing LPL activity seen in animal studies were not observed in the limited human studies. Such adipogenic effects of GIP appear to be more pronounced during insulin deficiency. GIP may also be pro-inflammatory in adipose tissue but evidence on this is still weak. GIP probably has a role in modulating other body fat deposits such as promoting accumulation of visceral and liver fat. While GIP antagonism maybe a therapeutic approach to prevent adiposity, the metabolic benefits of GIP antagonism seen in animal studies have not been tested in humans. Promising results have been obtained with combination of GIP and GLP-1 receptor agonists and we await with interest the results of future studies of GIP antagonists in humans.

**Highlights**

**• GIP increases adipose tissue blood flow, lipoprotein lipase activity and storage of triacylglycerol in human adipose tissue**

**• GIP may increase pro-inflammatory adipokines and adipose tissue inflammation.**

**• Excess GIP secretion may contribute to the development of fatty liver and NAFLD.**

**• Treatment with GIP alone has no glucose lowering benefits in type 2 diabetes.**

**• Combined GIP/GLP-1 agonist has greater effect on improving glycaemic and weight reduction over GLP-1 agonist alone.**

**Glossary**

ATBF: Adipose tissue blood flow

ATGL: adipose tissue triglyceride lipase

DNL: *de novo* lipogenesis

HSL: hormone sensitive lipase

IMCL: Intramyocellular lipid

LPL: Lipoprotein lipase

NEFA: non esterified fatty acids

NAFLD: Non-alcoholic fatty liver disease

TAG: triacylglycerol

T2D : Type 2 diabetes

**Figure legends**

**Figure 1** Schematic diagram illustrating postprandial lipid metabolism.

Dietary lipids are absorbed in the small intestine and absorbed systemically: most are stored in SAT and VAT as TAG; the remainder are oxidised in skeletal muscle and liver. Excess lipids/NEFA (spill over) are stored in the visceral adipose tissue and non-adipose tissues (liver, pancreas and skeletal muscle).

LPL, Lipoprotein lipase; ATGL, adipose tissue triglyceride lipase; HSL, hormone sensitive lipase); TAG, triacylglycerols; NEFA, non-esterified fatty acids; DNL, *de novo* lipogenesis; IMCL, Intramyocellular lipid; subcutaneous adipose tissue (SAT); visceral adipose tissue (VAT). + denotes stimulation, – denotes inhibitory action.

**Figure 2:** Schematic diagram illustrating the effects of GIP on lipid metabolism in adipose and non-adipose tissues.

GIP increases adipose tissue blood flow providing more triacylglycerol (TAG) substrate and promotes lipogenesis by enhancing lipoprotein lipase (LPL) [shown in the upper half of adipose tissue cartoon]. GIP also increases lipolysis by enhancing inflammatory adipokines and hormone sensitive lipase (HSL) [lower half of cartoon]. GIP increases liver fat accumulation possibly through suppressor of inflammatory cytokine signaling (SOCS) pathways involving inflammatory adipokines. GIP is also known to increase oxidation of TAG in the cardiomyocytes in mice models. GIP may have indirect effects on ectopic fat deposition in pancreas and skeletal muscle. NEFA, non-esterified fatty acids; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; IMCL, Intramyocellular lipid.

**Conflict of interest**

The authors declare no specific conflict of interest in relation to this review. JPHW and DJC disclose honoraria and institutional grants from several pharmaceutical companies developing or marketing medicines used for the treatment of diabetes and obesity unrelated to this review.

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