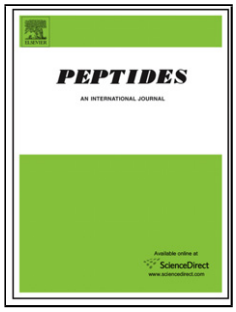

GIP analogues and the treatment of obesity-diabetes

Clifford J. Bailey

PII: S0196-9781(19)30180-9

DOI: https://doi.org/10.1016/j.peptides.2019.170202

Reference: PEP 170202

To appear in: *Peptides*

Received Date: 11 October 2019

Revised Date: 9 November 2019

Accepted Date: 11 November 2019

Please cite this article as: Bailey CJ, GIP analogues and the treatment of obesity-diabetes, *Peptides* (2019), doi: https://doi.org/10.1016/j.peptides.2019.170202

GIP analogues and the treatment of obesity-diabetes

Clifford J. Bailey*

School of Life and Health Sciences, Aston University, Birmingham, UK

Correspondence to:
Professor Clifford J. Bailey,
School of Life and Health Sciences,
Aston University,
Birmingham B4 7ET, UK
c.j.bailey@aston.ac.uk
Tel. +44 (0) 121 204 3898

3743 words of text

Highlights

- Analogues of glucose-dependent insulinotropic polypeptide (GIP) with agonist or antagonist effects at the GIP receptor have been developed.
- Studies in rodents have noted that both reduced and enhanced activity of GIP can prevent or reverse obese non-insulin dependent forms of diabetes.
- Species differences in GIP receptor responsiveness have complicated the extrapolation of evidence from rodents to humans.
- Clinical studies have shown the potential of GIP receptor agonists to be used in combination with other glucose-lowering peptides in the treatment of obese type 2 diabetes.

Abstract

The potential application of glucose-dependent insulinotropic polypeptide (gastric inhibitory polypeptide, GIP) in the management of obesity and type 2 diabetes has been controversial. Initial interest in the therapeutic use of GIP was dampened by evidence that its insulinotropic activity was reduced in type 2 diabetes and by reports that it increased glucagon secretion and adipose deposition in non-diabetic individuals. Also, attention was diverted away from GIP by the successful development of glucagon-like peptide-1 (GLP-1) receptor agonists, and a therapeutic strategy for GIP became uncertain when evidence emerged that both inhibition and enhancement of GIP action could prevent or reverse obese non-insulin dependent forms of diabetes in rodents. Species differences in GIP receptor responsiveness complicated the extrapolation of evidence from rodents to humans, but initial clinical studies are investigating the effect of a GIP antagonist in non-diabetic individuals. A therapeutic role for GIP agonists was reconsidered when clinical studies noted that the insulinotropic effect of GIP was increased if near-normal glycaemia was re-established, and GIP was found to have little effect on glucagon secretion or adipose deposition in obese type 2 diabetes patients. This encouraged the development of designer peptides that act as GIP receptor agonists, including chimeric peptides that mimic the incretin partnership of GIP with GLP-1, where the two agents exert complementary and often additive effects to improve glycaemic control and facilitate weight loss. Polyagonist peptides that exert agonism at GIP, GLP-1 and glucagon receptors are also under investigation as potential treatments for obese type 2 diabetes.

Introduction

After the discovery of gastric inhibitory polypeptide (glucose-dependent insulinotropic polypeptide; GIP) evidence soon emerged to show that this hormone contributed to more physiological effects than the inhibition of gastric acid secretion [1, 2]. Potentiation of nutrient-induced insulin release secured a place for GIP alongside glucagon-like peptide-1 (GLP-1) as an incretin hormone, and reports of a reduced incretin effect in type 2 diabetes mellitus raised the possibility that GIP might offer a therapeutic opportunity to restore the incretin effect [3-5]. Moreover, GIP enhanced first-phase glucose-induced insulin secretion in non-diabetic individuals and promoted proliferation of islet beta-cells in rodent models and insulin-secreting cell lines [6]. However, the insulin-releasing effect of GIP was diminished in type 2 diabetes, whereas the insulin-releasing potency of GLP-1 was largely retained in type 2 diabetes, and GLP-1 additionally exerted a satiety effect and suppressed prandial glucagon secretion [7-9]. Also, meal-stimulated GIP concentrations were similar in people with and without type 2 diabetes, whereas GLP-1 concentrations were reduced in type 2 diabetes, providing an opportunity to preferentially raise GLP-1 concentrations as a treatment strategy [5, 9, 10]. Thus,

interest in a possible therapeutic role for GIP was over-shadowed by the development of GLP-1 receptor agonists. The therapeutic strategy for GIP also became undecided when inhibition of GIP action as well as administration of excess GIP were both shown to prevent or reverse obese non-insulin dependent forms of diabetes in rodents [11]. However, recent clinical studies have identified potential benefits of GIP in combination with GLP-1, and this review examines the evidence and evaluates the opportunities for GIP-based therapies in the treatment of type 2 diabetes.

Physiological studies in human obesity and type 2 diabetes

An increased density of GIP-producing K-cells has been observed in the duodenum of type 2 diabetes patients, but this does not appear to significantly alter GIP responses to an oral glucose challenge [10, 12]. A meta-analysis of 23 studies found generally similar peak GIP concentrations with only a marginally lower incremental area-under-the-curve of GIP concentrations in response to nutrient stimulation in subjects with type 2 diabetes compared to non-diabetic controls [10]. It is noted, however, that GIP secretion is highly sensitive to the types and amounts of nutrients ingested, previous diet and the rate of gastric emptying: thus each of these variables could obscure subtle alterations of GIP secretion in type 2 diabetes [13-16]. While the ability of GIP to enhance nutrient-induced insulin release is reduced in type 2 diabetes, this is most evident in severely hyperglycaemic patients, suggesting that this probably reflects the impaired functional status of the beta-cells in these patients rather than a defect of GIP action [17, 18]. Also, the ability of GIP to enhance the acute (first phase) insulin response is better preserved in type 2 diabetes than the later (second phase) response. The therapeutic relevance of this is that loss of the first phase nutrient-induced insulin response is an early feature of defective beta-cell function in type 2 diabetes, and restoring the acute response is known to considerably improve prandial glycaemic control [19].

Nutrient-stimulated GIP secretion in obese subjects is similar or higher than non-obese controls, but is often reduced with coexistent type 2 diabetes, although findings have not been consistent and appear to vary with the extent of hyperglycaemia and the time period studied after nutrient intake [10, 16-18, 20]. Nevertheless, a protracted reduction of calorie intake with weight loss is generally associated with increased meal-stimulated GIP secretion and an increased insulin response [20, 21].

Evidence from bariatric procedures

In obese non-diabetic individuals, gastric banding with reduced food intake has mostly decreased GIP concentrations, whereas vertical sleeve gastrectomy with rapid delivery of gastric content into the duodenum has generally raised acute GIP responses, although studies have not been consistent [22-28]. Roux-en-Y gastric bypass (RYGB), which diverts food from a small gastric pouch into the jejunum, has been variously reported to increase, decrease or have no effect on meal-stimulated GIP

concentrations, and no obvious correlation with the extent of improved glycaemic control has been identified amongst individuals with type 2 diabetes [25, 29-32]. Improved glycaemic control after RYGB has been attributed in large part to increased concentrations of GLP-1 and possibly peptide YY that result from rapid delivery of nutrients into the distal small intestine [33-35]. No relationship has been found between changes in glycaemic control and the reduction in GIP concentrations after surgical removal of the duodenum [36], and although hydrothermal ablation of the duodenal mucosa can reduce hyperglycaemia in type 2 diabetes this has not been compared with GIP concentrations [37]. Thus physiological and bariatric studies in humans have not identified a clear therapeutic strategy for GIP in the treatment of obesity or type 2 diabetes.

Experimental studies

Genetic obesity-diabetes syndromes in mice that are caused by defects of leptin production or action (notably *ob/ob* and *db/db* mutants) and diet-induced murine obesity and glucose intolerance are associated with hyperplasia of duodenal K-cells, increased GIP content of the duodenum and increased GIP concentrations [38, 39]. Interruption of GIP production by administration of GIP receptor antagonists, antibodies against GIP or against the GIP receptor can partially reduce or reverse the obesity, hyperglycaemia, hyperinsulinaemia and insulin resistance in these animal models, and reduce glucagon and corticosterone concentrations [40-45]. Also, GIP receptor knockout (Gipr(-/-)) prevented the development of diet-induced obesity in mice and reduced weight gain in *ob/ob* mice, consistent with the effect of GIP receptor antagonists [46]. However, there are small differences in the amino acid sequences of human GIP compared with rat GIP and mouse GIP (Figure 1), and the human GIP receptor has only 81% homology with rat and mouse GIP receptors [47]. These structural differences are associated with important functional differences. For example, whereas rat GIP receptor antagonists such as rat GIP(3-30) exert a strong competitive antagonist effect in rodents, human GIP(3-30) exerts little or no antagonism against the rat or mouse GIP receptor [48, 49]. Moreover, human (Pro3)GIP acts as an antagonist at the rat and mouse GIP receptors but acts as an agonist at the human GIP receptor [47-49]. Thus species differences of GIP receptor responsiveness to GIP antagonists make it difficult to extrapolate antagonist evidence from rodent models to man. Regarding surgical information between species, a RYGB procedure in diet-induced obese mice reduced the obesity and decreased GIP production by the Roux-limb, but not by the biliopancreatic limb of the intestine, and the serum GIP response was maintained [50]. This supports the view that different GIP responses to feeding after RYGB in human subjects may reflect differences in the length of the Roux limb and the adaptations of the mucosa.

Although the foregoing experimental evidence indicates that inactivation of GIP can reduce obesity and improve glycaemic control in mice, administration of stable long-acting forms of GIP to rodent

models can also improve glycaemic control, mostly without a significant effect on body weight. This is attributed to increased insulin secretion, increased β-cell mass and a reduced effect of C-terminally modified GIP on adipose deposition [51-54]. Moreover, transgenic mice that over-express GIP and show improved glycaemic control and increased β-cell function, also show reduced diet-induced obesity [55]. GIP has been variously reported to increase feeding or have no effect on feeding although intracerebroventricular administration of GIP decreased food intake and body weight in normal mice, possibly acting centrally by altering sensitivity to leptin [56-58]. Potent GIP receptor agonists also decreased food intake and body weight in diet-induced obese mice [58].

Early development of GIP analogues

Although the clinical investigation of GIP analogues has lagged far behind that of GLP-1 analogues, early development proceeded largely in parallel. When studies in Coleraine led by Peter Flatt noted that the dipeptidyl peptidase-4 (DPP-4) degradation product GIP(3-42) was less potent than native GIP(1-42) *and* antagonised the effect of native GIP(1-42), the group examined a series of N-terminally modified GIP analogues and found that modifications at N1 or N2 generally conferred DPP-4 resistance and enhanced insulin releasing and anti-hyperglycaemic activity [59-62]. However, amino acid substitution at N3 reduced biological activity and antagonised the action of native GIP(1-42) [11]. To increase the stability of GIP, D-Ala2 substitution, acylation and PEGylation were undertaken and the potential therapeutic application of these molecules was studied in rodent models [63-67].

Because experimental studies in obese-diabetic rodents indicated that both increased and decreased activity of GIP receptors can improve glycaemic control with or without concurrent weight loss, it was uncertain which therapeutic strategy to adopt: GIP antagonism or agonism? Moreover, differences in the activation and inhibition of GIP receptors between rodents and humans complicated the extrapolation of rodent studies into a clinical context [68, 69]. To address this, detailed analyses of structure-activity relationships for native GIP and variant GIP molecules have been undertaken using an assay of cAMP production by Chinese hamster ovary (CHO) cells and monkey kidney (COS) cells transfected with cDNA to express human GIP receptors [70, 71]. These studies determined that the biological activity of GIP resides with the N-terminal 1-14 sequence of residues, while the middle region (residues 19-30) can improve binding affinity and C-terminal residues (31-42) appear to contribute conformational advantage to the molecule [Figure 1].

GIP antagonism

Although the anti-obesity and anti-hyperglycaemic effects of GIP inhibition in rodents fuelled interest in the therapeutic potential of GIP antagonists, detailed evaluation of such agents in obese-diabetic

patients has yet to take place. In vitro studies established that truncations, deletions or substitutions along the 1-14 sequence of human GIP results in molecules with very weak partial agonism or no agonism, and some of these molecules have shown biological antagonism of human GIP receptor function. GIP(3–30) and GIP(5–30) are reported to be the most potent competitive antagonists at human GIP receptors, and the antagonistic effect of GIP(3-30) is increased when competing against GIP molecules that lack a C-terminal region [71]. Thus, although endogenous active circulating GIP(1-42) is degraded by DPP-4 to GIP(3-42), which has a competitive antagonist effect at the GIP receptor, the C-terminal residues of GIP may partially protect against this antagonism [71, 72]. GIP may also be degraded by neutral endopeptidases and several truncated GIP variants such as GIP(6–30) and GIP(7–30) have been identified. These act as GIP receptor antagonists in rodents, but have little effect at human GIP receptors [73-75]. A long-acting GIP antagonist [palmitoylated human GIP(3–30), with a C-terminal extension based on the GLP-1 receptor agonist exendin], promoted weight loss and improved glycaemic control in fat-fed mice [76]. However, an infusion of human GIP(3-30) in healthy non-diabetic subjects significantly reduced the insulin response and increased glucose excursions, confirming that inhibiting GIP action raises blood glucose in non-diabetic humans [77, 78]. The clinical effect of inhibiting GIP action with GIP(3-30) was compared to inhibiting GLP-1 action with exendin(9-39), and it was concluded that GIP may normally provide a greater stimulus for insulin secretion than GLP-1 [78]. The effect of GIP receptor antagonism in human type 2 diabetes remains to be established.

GIP agonism

Recent clinical interest in the potential therapeutic opportunities of GIP agonism was encouraged by evidence that the insulinotropic potency of GIP is increased when near-normal glycaemia is established in type 2 diabetes patients receiving insulin [79-81]. Although this might reflect in part a sparing effect on the beta cells, the first phase glucose-induced insulin response is enhanced by GIP and glucagon secretion is only increased at low glucose concentrations, improving the counterregulatory response to hypoglycaemia [81]. The need to first re-establish near normal glycaemia points to the use of GIP in combination with another glucose-lowering agent: indeed the effect of chronic administration of GIP alone or a potent GIP receptor agonist alone in obese type 2 diabetes patients has not been established. While GIP may increase adipose deposition in lean human subjects, partly due to increased vascular perfusion of adipose tissue, this effect appears to be diminished in non-diabetic obese individuals, suggesting that GIP does not promote adipose deposition in human obesity [82, 83]. A further property ascribed to GIP is that of improved bone health through inhibition of bone resorption [84]. This is consistent with the decrease in bone mineral density, decreased bone strength, decreased cortical thickness and increased osteoclast activity in GIP receptor knockout mice [85, 86].

The foregoing provides evidence to support the therapeutic value of GIP agonism in combination with at least one other glucose-lowering agent in the treatment of hyperglycaemia in humans. But why should the diametrically opposite approaches of GIP agonism *and* GIP antagonism improve obesity-diabetes status in rodent models? Suggestions in the literature include the possibility that chronic exposure to GIP receptor agonists might cause desensitisation of the GIP receptor through receptor down-regulation which reduces the effect of GIP, and/or degradation products of GIP might antagonise receptor function [87]. Whether such ideas could be extrapolated to human type 2 diabetes remains a further conjecture, but it is suggested that if GIP antagonists can improve glucose homeostasis without enhancing insulin secretion, then other glucose-lowering mechanism must be taking place [41-43]. Possible effects on other aspects of metabolism, hunger-satiety behaviour and exercise remain to be clarified.

GIP therapy in combination with GLP-1

Many of the potential benefits of GIP administration are complementary to those of GLP-1, and use of the two hormones together could offer advantages for the treatment of obese type 2 diabetes. Both hormones contribute to the incretin effect to enhance prandial insulin secretion, and they may act on the islet beta-cells in part through different and partially additive mechanisms [88]. Both can promote beta-cell mass in vitro and in animal models but this has yet to be clearly shown in type 2 diabetes patients. The suppressive effect of GLP-1 on glucagon secretion should moderate a possible tendency for high GIP concentrations to increase glucagon secretion without hypoglycaemia, and the satiety and weight loss effects of GLP-1 should counter the possibility that GIP might increase adipose deposition as seen in lean individuals. Both hormones promote bone health and have been reported to confer benefits against age-related cognitive decline [89]. GLP-1 is already established as an effective therapy for obese type 2 diabetes and chimeric designer peptides provide a means to achieve agonism at both GLP-1 and GIP receptors with the same molecule [90-92].

Studies in diet-induced obese and genetically obese diabetic rodents have noted that administration of GIP or GIP analogues with potent GIP receptor agonism can increase the weight-reducing, insulin-releasing and blood glucose-lowering effects of GLP-1 [90-95]. Also, GLP-1 and GIP together increased energy expenditure and did not promote appetite in rodent models, while a study in overweight and obese non-diabetic subjects has indicated that GIP might reduce the satiety effect of GLP-1 [96]. Initial ‘proof of principle’ studies in non-diabetic and type 2 diabetic subjects using peptides with agonistic effects at GIP and GLP-1 receptors recorded similar or greater glucose-lowering activity than equivalent doses of a GLP-1 receptor agonist alone [91, 92]. For example, a GIP/GLP-1 dual agonist with the catchy nickname ‘twincretin’, which incorporates substantial N-terminal homology with GIP and C-terminal homology with the GLP-1 receptor agonist exenatide,

produced a dose dependent decrease in HbA1c over 6 weeks in type 2 diabetes subjects (Figure 2) [91, 92, 97]. To protect against enzymatic degradation by DPP-4, the twincretin has aminoisobutyric acid at N2, and to further prolong the active form in the circulation there is a fatty acid link at the C-terminus to attach to albumin. Several other GIP/GLP-1 dual agonist peptides have now been reported, including the N-ac(d-Ala2)GIP/GLP-1-exe hybrid which has D-Ala at N2 to protect against DPP-4 degradation and C-terminal homology with exenatide [95]. This dual agonist has been shown to decrease HbA1c and body weight in high fat fed mice, and increase beta-cell mass, pancreatic insulin content and insulin responsiveness.

The most extensively studied GIP/GLP-1 dual agonist is tirzepatide (LY3298176). This 39 amino acid peptide is based on the biologically active N-terminal GIP(1-14) sequence with an N2 aminoisobutyric acid substitution (Figure 2) [98]. The mid-sequence contains substitutions compatible with GLP-1 receptor agonism and there is a C20 fatty diacid chain linked via glutamic acid to the Lys20 residue to facilitate attachment to albumin to prolong viability in the circulation. There is also an amidated exenatide-like C-terminal sequence. The structure confers stronger agonism for the GIP receptor than the GLP-1 receptor: binding affinity for the GIP receptor is similar to native GIP(1-42), but about 5-fold weaker for the GLP-1 receptor than native GLP-1. This provides a degree of balance that takes account of the physiologically higher circulating concentrations of GIP than GLP-1. The modifications that reduce enzymatic degradation provide sufficient durability for once-weekly subcutaneous administration. Preclinical studies in rodent models indicated that the peptide could increase beta-cell function more than GIP agonism or GLP-1 agonism alone, reduce food intake and body weight, and increase energy expenditure [98].

The preclinical observations were confirmed in humans: initial 1-month trials with tirzepatide in healthy subjects and people with type 2 diabetes noted improved oral glucose tolerance, an increased insulin response to oral glucose and reduced body weight in a dose-dependent manner [98]. In a phase 2 double-blind placebo-controlled study, 316 type 2 diabetes patients treated by lifestyle $\pm$ metformin (baseline HbA1c 8.2%, body weight 92 kg and BMI 32 kg/m^2) were randomised to once weekly subcutaneous injection of tirzepatide (1, 5, 10, and 15 mg), dulaglutide (1.5 mg) or placebo for 26 weeks [99]. Compared to placebo, tirzepatide was associated with dose related mean reductions in HbA1c of 1·00%, 1·67%, 1·83% and 1·89% for the 1,5,10 and 15mg doses respectively. Dulaglutide reduced HbA1c by 1·21% in this study suggesting that high doses of tirzepatide exerted considerably greater glucose-lowering efficacy than the maximum dose of dulaglutide in routine clinical use. Tirzepatide was also associated with a marked dose-dependent loss of body weight (by 0·9 kg with the 1 mg dose to 11·3 kg with the 15 mg dose) versus reductions of 2·7 kg for dulaglutide and 0·4 kg for placebo. Small reductions in circulating triglyceride concentrations and a marginal

reduction in blood pressure were also noted with tirzepatide, and there was no change in the incidence of cardiovascular events or hypoglycaemia.

Set against the efficacy of high doses of tirzepatide is a high incidence of gastrointestinal disturbances, although these were mostly early and transient. Also of note, over half of patients receiving the 15mg dose of tirzepatide developed antibodies to this agent, but these were generally of low titre and did not appear to compromise efficacy.

Preliminary accounts of the effects of several other GIP/GLP-1 dual agonist peptides in healthy subjects and type 2 diabetes patients have been reported, eg once-daily injection of RG7697 (MAR709) and NNC0090-2746 [82-85, 103]. These accounts confirm that GIP receptor agonism does not interrupt the glucose-lowering or weight-lowering effects of GLP-1 receptor agonism, and may provide additional efficacy, but not with the same potency as the long-acting once-weekly agent tirzepatide.

GIP as part of a triple agonist

Triple agonist (triagonist) peptides with stimulatory effects at the glucagon, GLP-1 and GIP receptors (GcgR/GLP-1R/GIPR) have been developed with a balance of activation at the three receptors. Their structures are largely based on the amino acid sequence of glucagon with positional modifications, and their activity at each of the receptors has been assessed in vitro. Each has shown strong glucose-lowering and weight-lowering effects in rodents and/or monkeys [93, 97, 104, 105]. Examples of triagonists are shown in Figure 2. Weight-lowering was particularly effective with some triagonists which may be attributable to the inclusion of glucagon agonism: glucagon exerts a satiety effect and promotes energy expenditure. It is anticipated that the glucose-lowering effects conferred by the GLP-1 and GIP components of the triagonists are more than compensating for the effect of glucagon receptor agonism to promote endogenous glucose production. Triagonists can also reduce hepatic lipid stores in animal models: this favours use in the treatment of hepatic steatosis, noting that the removal of ectopic hepatic fat is a feature of the success of calorie restricted diets in the early treatment of obese type 2 diabetes [106].

In principle, designer polyagonist molecules offer the opportunity to produce a variety of amino acid sequences with different activities at different receptors. This could enable glucose-lowering and weight-lowering potencies to be selected to closely align with the therapeutic needs of the individual - a move towards precision medicine with a single molecule. By simultaneously targeting multiple receptors it should be possible to achieve treatment goals with lower dose-equivalents than required if only one or two differently acting agents is used. Also, lesser effects at several receptors should reduce the side effects associated with a high dose of one agent, although the levels of receptor

activation required to produce the therapeutic effects might lead to long-term desensitisation, or incur risk of anaphylactic reactions [107]. Production cost and maintaining the physico-chemical stability of large peptides in injection media can be a challenge, and a particular caution resides with the immunogenicity of non-native peptide sequences and the development of antibodies as already seen with tirzepatide [98, 99].

Many gastro-intestinal peptides with different effects on glucose homeostasis could be considered for therapeutic use in the management of obesity and type 2 diabetes, as agonists and antagonists, with or without GIP (table 1). Effects of mixtures, hybrids and chimeras exerting agonist effects of these peptides without affecting GIP receptors have received preliminary assessment in obese and diabetic animal models, and several have proceeded into clinical development [103]. Combined peptide-steroid molecules have also been developed, and formulations for enteral as well as parenteral administration continue to receive attention. With a view to the long-term future it is possible that glucose-responsive (so-called 'smart') formulations could be devised to release the active agent(s) within the body to coincide with changes in blood glucose [107].

Conclusion

Therapeutic aspirations for GIP receded into the shadow of its incretin partner GLP-1 after the insulinotropic potency of GIP was shown to be much reduced in type 2 diabetes. It was also difficult to reconcile evidence that *both* an increase *and* a decrease in GIP action could prevent or reverse obese non-insulin dependent diabetes in rodents. Clinical attention to the therapeutic potential of GIP was rekindled after studies identified species differences in GIP receptor responsiveness and noted that the insulinotropic potency of GIP returned in type 2 diabetes patients when near normal glycaemia was re-established. The complementary effects of GIP and GLP-1 to enhance nutrient-induced insulin release while facilitating weight loss are now being incorporated into designer peptides,

Funding source

No specific funding source is identified.

Conflict of interest

The author declares no specific conflict of interest for this review, but discloses research support, honoraria, and ad hoc advisory activities associated with several pharmaceutical companies interested in the treatment of diabetes and obesity.

References

1. Brown JC, Dryburgh JR. A gastric inhibitory polypeptide. Can J Biochem 1971; 49: 867–872.
2. Brown JC, Dryburgh JR, Ross SA, Dupré J. Identification and actions of gastric inhibitor polypeptide. Recent Prog Horm Res. 1975; 31: 487-532.
3. Dupre J, Ross SA, Watson D, Brown JC. Stimulation of insulin secretion by gastric inhibitory polypeptide in man. J Clin Endocrinol Metab 1973, 37, 826-8
4. Creutzfeldt, W. 1979. The incretin concept today. Diabetologia 1979, 16:75-85.
5. Nauck M, Stöckmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. Diabetologia 1986, 29, 46–52.
6. Meier JJ, Nauck MA: Glucose-dependent insulinotropic polypeptide/gastric inhibitory polypeptide. Best Pract Res Clin Endocrinol Metab 2004, 18: 587-606.
7. Vilsboll T, Krarup T, Deacon CF, Madsbad S, Holst JJ. Reduced postprandial concentrations of intact biologically active glucagon-like peptide 1 in type 2 diabetic patients. Diabetes 2001, 50, 609-13.
8. Nauck MA, Heimesaat MM, Orskov C, Holst JJ, Ebert R, Creutzfeldt W (1993) Preserved incretin activity of glucagon-like peptide 1 [7–36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. J Clin Invest 1993, 91:301–307.
9. Nauck MA, Baller B, Meier JJ. Gastric inhibitory polypeptide and glucagon-like peptide-1 in the pathogenesis of type 2 diabetes. Diabetes 2004; 53 (suppl 3): S190-S196
10. Calanna S, Christensen M, Holst JJ, Laferrère B, Gluud LL, Vilsbøll T et al. Secretion of glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. Systematic review and meta-analysis of clinical studies. Diabetes Care 2013; 36: 3346-3352.
11. Irwin N, Flatt PR. Therapeutic potential for GIP receptor agonists and antagonists. Best Pract Res Clin Endocrinol Metab 2009; 23: 499-512.
12. Theodorakis MJ1, Carlson O, Michopoulos S, Doyle ME, Juhaszova M, Petraki K et al. Human duodenal enteroendocrine cells: source of both incretin peptides, GLP-1 and GIP. Am J Physiol Endocrinol Metab 2006; 290: E550-9.
13. Elliott RM, Morgan LM, Tredger JA, Deacon S, Wright J, Marks V. Glucagon-like peptide-1 (7-36)amide and glucose-dependent insulinotropic polypeptide secretion in response to nutrient ingestion in man: acute post-prandial and 24-h secretion patterns. J Endocrinol 1993; 138: 159-66.

14. Knapper JME, Morgan LM, Fletcher JM. Nutrient-induced secretion and metabolic effects of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1. Proc Nutrition Soc 1996, 55, 291-305.

15. Marathe CS, Rayner CK, Jones KL, Horowitz M. Relationship between gastric emptying, postprandial glycemia and incretin hormones. Diabetes Care 2013, 30, 1396-1405.

16. Vilsbøll T, Krarup T, Sonne J, Madsbad S, Vølund A, Juul AG, Holst JJ. Incretin secretion in relation to meal size and body weight in healthy subjects and people with type 1 and type 2 diabetes mellitus. J Clin Endocrinol Metab 2003; 88: 2706-13.

17. Vilsbøll T. Krarup T, Madsbad S, Holst JJ. Defective amplification of the late phase insulin response to glucose by GIP in obese Type II diabetic patients. Diabetologia 2002, 45: 1111–19.

18. Vilsbøll T, Knop FK, Krarup T, Johansen A, Madsbad S, Larsen S, Hansen T, Pedersen O, Holst JJ. The pathophysiology of diabetes involves a defective amplification of the late-phase insulin response to glucose by glucose-dependent insulinotropic polypeptide—regardless of etiology and phenotype. J Clin Endocrinol Metab 2003, 88, 4897–4903.

19. Kahn SE, Zraika S, Utzschneider KM, Hull RL. The beta cell lesion in type 2 diabetes: there has to be a primary functional abnormality. Diabetologia 2009; 52: 1003–1012.

20. Creutzfeldt W, Ebert R, Willms B, Frerichs H, Brown JC. Gastric inhibitory polypeptide (GIP) and insulin in obesity: increased response to stimulation and defective feedback control of serum levels. Diabetologia 1978; 14: 15-24.

21. Verdich C, Toubro S, Buemann B, Madsen JL, Holst JJ, Astrup A. The role of postprandial releases of insulin and incretin hormones in meal-induced satiety—effect of obesity and weight reduction. Int J Obesity 2001, 25, 1206–1214.

22. Cho Y M, Kieffer T J. K cells and glucose-dependent insulinotropic polypeptide in health and disease. Vits Hormones 2010, 84, 111-150.

23. Otten J, Ryberg M, Mellberg C, Andersson T, Chorell T, Lindahl B, et al. Postprandial levels of GLP-1, GIP and glucagon after 2 years of weight loss with a Paleolithic diet: a randomised controlled trial in healthy obese women. European J Endocrinol 2019, 180, 417-27

24. Shak JR, Roper J, Perez-Perez GI, Tseng CH, Francois F, Gamagaris Z et al. The effect of laparoscopic gastric banding surgery on plasma levels of appetite-control, insulinotropic, and digestive hormones. Obes Surg. 2008; 18: 1089–96.

25. Rodieux F, Giusti V, D'Alessio DA, Suter M, Tappy L Effects of Gastric Bypass and Gastric Banding on Glucose Kinetics and Gut Hormone Release. Obesity 2008, 16, 298-305.

26. Rao RS, Kini S. GIP and bariatric surgery. Obes Surg 2011; 21: 244-52.

27. Farey JE, Preda TC, Fisher OM, Levert-Mignon AJ, Stewart RL, Karsten E, et al. Effect of laparoscopic sleeve gastrectomy on fasting gastrointestinal, pancreatic, and adipose-derived hormones and on non-esterified fatty acids. Obes Surg 2017; 27: 399–407.

28. Bunt JC, Blackstone R, Thearle MS, Vinales KL, Votruba S, Krakoff J. Changes in glycemia, insulin and gut hormone responses to a slowly ingested solid low-carbohydrate mixed meal after laparoscopic gastric bypass or band surgery. Int J Obes. 2017; 41: 706–713.

29. Korner J, Bessler M, Inabnet W, Taveras C, Holst JJ. Exaggerated glucagon-like peptide-1 and blunted glucose-dependent insulinotropic peptide secretion are associated with Roux-en-Y gastric bypass but not adjustable gastric banding. Surg Obes Relat Dis. 2007; 3: 597–601.

30. Laferrère B. Bariatric surgery and obesity: influence on the incretins. Int J Obes 2016; 6 (Suppl 1): S32–S36

31. Meek CL Lewis HB, Reimann F, Gribble FM, Park AJ. The effect of bariatric surgery on gastrointestinal and pancreatic peptide hormones. Peptides 2016, 77, 28-37.

32. Svane MS, Bojsen-Møller KN, Nielsen S, Jørgensen NB, Dirksen C, Bendtsen F, et al. Effects of endogenous GLP-1 and GIP on glucose tolerance after Roux-en-Y gastric bypass surgery. Am J Physiol 2016, 310, E505-E514

33. Holst JJ, Madsbad S. Mechanisms of surgical control of type 2 diabetes: GLP-1 is key factor. Surgery Obesity Related Diseases 2016, 12, 1236-1242.

34. Hutch CR, Sandoval D. The role of GLP-1 in the metabolic success of bariatric surgery. Endocrinology, 2017, 158, 4139–4151,

35. Larraufie P, Roberts GP, McGavigan AK, Hardwick RH, Reimann F, Gribble FM. Important Role of the GLP-1 axis for glucose homeostasis after bariatric surgery. Cell Reports 2019, 26, 1399–1408.

36. Muscogiuri G, Mezza T, Prioletta A, Sorice GP, Clemente G, Sarno G, et al. Removal of duodenum elicits GLP-1 secretion. Diabetes Care 2013; 36: 1641-1646.

37. Cherrington AD, Rajagopalan H, Maggs D, Deviere J. 2017 Hydrothermal duodenal mucosal resurfacing: role in the treatment of metabolic disease. Gastrointestinal Endoscopy Clinics of North America 2017, 27, 299–311.

38. Flatt PR, Bailey CJ, Kwasowski P, Swanston-Flatt SK, Marks V. Abnormalities of GIP in spontaneous syndromes of obesity and diabetes in mice. Diabetes 1983; 32: 433-5.

39. Bailey CJ, Flatt PR, Kwasowski P, Powell CJ, Marks V. Immunoreactive gastric inhibitory polypeptide and K cell hyperplasia in obese hyperglycaemic (ob/ob) mice fed high fat and high carbohydrate cafeteria diets. Acta Endocrinol (Copenh) 1986; 112: 224-9.

40. Gault VA, O'Harte FPM, Harriott P, Mooney MH, Green BD, Flatt PR. Effects of the novel (Pro3)GIP antagonist and exendin(9–39)amide on GIP- and GLP-1-induced cyclic AMP generation, insulin secretion and postprandial insulin release in obese diabetic (ob/ob) mice: evidence that GIP is the major physiological incretin. Diabetologia 2003, 46, 222–230.

41. Gault VA, Irwin N, Green BD, McCluskey JT, Greer B, Bailey CJ, et al. Chemical ablation of gastric inhibitory polypeptide receptor action by daily (Pro3)GIP administration improves glucose tolerance and ameliorates insulin resistance and abnormalities of islet structure in obesity-related diabetes Diabetes 2005, 54,. 2436-2446.

42. Irwin N, McClean PL, O'Harte FPM, Gault VA, Harriott P, Flatt PR. Early administration of the glucose-dependent insulinotropic polypeptide receptor antagonist (Pro3)GIP prevents the development of diabetes and related metabolic abnormalities associated with genetically inherited obesity in ob/ob mice. Diabetologia 2007, 50, 1532-1540.

43. McClean PL, Irwin N, Cassidy RS, Holst JJ, Gault VA, Flatt PR. GIP receptor antagonism reverses obesity, insulin resistance, and associated metabolic disturbances induced in mice by prolonged consumption of high-fat diet. Am J Physiol Endocrinol Metab 2007; 293: E1746–E1755

44. Irwin N, McClean PL, Patterson S, Hunter K, Flatt PR. Active immunisation against gastric inhibitory polypeptide (GIP) improves blood glucose control in an animal model of obesity-diabetes. Biol Chem 2009, 390, 75-80.

45. Nasteska D, Harada N, Suzuki K, Yamane S, Hamasaki A, Joo E, et al. Chronic reduction of GIP secretion alleviates obesity and insulin resistance under high-fat diet conditions. Diabetes 2014, 63: 2332–43.

46. Miyawaki K, Yamada Y, Ban N, Ihara Y, Tsukiyama K, Zhou H, et al. Inhibition of gastric inhibitory polypeptide signaling prevents obesity. Nature Med 2002; 8: 738–42. .

47. Sparre-Ulrich AH , Hansen LS, Svendsen B, Christensen M, Knop FK, Hartmann B, et al. Species-specific action of (Pro3)GIP—a full agonist at human GIP receptors, but a partial agonist and competitive antagonist at rat and mouse GIP receptors. Br J Pharmacol 2016; 173: 27-38

48. Gabe MBN, Sparre-Ulrich AH, Pedersen MF, Gasbjerg LS, Inoue A, Brauner-Osborne H, et al. Human GIP(3-30)NH2 inhibits G protein-dependent as well as G protein-independent signaling and is selective for the GIP receptor with high-affinity binding to primate but not rodent GIP receptors. Biochem Pharmacol 2018, 150, 97-107.

49 Sparre-Ulrich AH, Gabe MB, Gasbjerg LS, Christiansen CB, Svendsen B, Hartmann B, et al. GIP(3-30)NH2 is a potent competitive antagonist of the GIP receptor and effectively inhibits GIP-mediated insulin, glucagon, and somatostatin release. Biochem Pharmacol 2017; 131: 78-88.

50. Zhou J, Hao Z, Irwin N, Berthoud HR, Ye J. Gastric inhibitory polypeptide (GIP) is selectively decreased in the roux-limb of dietary obese mice after RYGB surgery. PLoS One 2015, 10:e0134728.

51. Widenmaier SB, Kim SJ, Yang GK, De Los Reyes T, Nian C, et al. A GIP receptor agonist exhibits beta-cell anti-apoptotic actions in rat models of diabetes resulting in improved beta-cell function and glycemic control. PLoS One 2010;5:e9590.

52. Herbach N, Bergmayr M, Göke B, Wolf E, Wanke R . Postnatal development of numbers and mean sizes of pancreatic islets and beta-cells in healthy mice and GIPR(dn) transgenic diabetic mice. PLoS One 2011;6:e22814.

53. Gault VA, Porter DW, Irwin N, Flatt PR. Comparison of sub-chronic metabolic effects of stable forms of naturally occurring GIP(1-30) and GIP(1-42) in high-fat fed mice. J Endocrinol 2011, 208: 265-71.

54. Tatarkiewicz K, Hargrove DM, Jodka CM, Gedulin BR, Smith PA, Hoyt JA, et al. A novel long-acting glucose-dependent insulinotropic peptide analogue: enhanced efficacy in normal and diabetic rodents. Diabetes Obes Metab 2014, 16: 75 – 85.

55. Kim SJ, Nian C, Karunakaran S, Clee SM, Isales CM, McIntosh CHS. GIP-overexpressing mice demonstrate reduced diet-induced obesity and steatosis, and improved glucose homeostasis. PLoS One 2012; 7: e40156.

56. Koong CN, Kim MS, Jang BT, Lee YH, Cho YM, Choi HJ. Central administration of GLP-1 and GIP decreases feeding in mice. Biochem Biophys Res Comm 2017, 490, 247-252.

57. Kaneko K, Fu Y, Lin HY, Cordonier EL, Mo Q, Gao Y, et al. Gut-derived GIP activates central Rap1 to impair neural leptin sensitivity during overnutrition. J Clin Invest 2019, 129. Epub ahead of print. https://doi.org/10.1172/JCI126107

58. Mroz PA, Finan B, Gelfanov V, Yang B, Tschöp MH, DiMarchi RD, et al. Optimized GIP analogs promote body weight lowering in mice through GIPR agonism not antagonism. Molecular Metab 2019, 20, 51-62.

59. Gault VA, Parker JC, Harriott P, Flatt PR, O'Harte FP. Evidence that the major degradation product of glucose-dependent insulinotropic polypeptide, GIP(3-42), is a GIP receptor antagonist in vivo. J Endocrinol 2002, 175: 525-33.

60. O'Harte FPM, Gault VA, Parker JC, Harriott P, Mooney MH, Bailey CJ, Flatt PR. Improved stability, insulin-releasing activity and antidiabetic potential of two novel N-terminal analogues of gastric inhibitory polypeptide: N-acetyl-GIP and pGlu-GIP. Diabetologia 2002, 45:1281-1291.

61. Gault VA, Flatt PR, Bailey CJ, Harriott P, Greer B, Mooney MH, O'Harte FPM. Enhanced cyclic AMP generation and insulin-releasing potency of two novel N-terminal Tyr1-modified enzyme resistant forms of GIP, is associated with significant antihyperglycaemic activity in spontaneous obesity-diabetes. Biochem J 2002, 367: 913-920.

62. Gault VA, Flatt PR, Harriott P, Mooney MH, Bailey CJ, O'Harte FPM. Improved biological activity of Gly2- and Ser2-substituted analogues of glucose-dependent insulinotropic polypeptide. J Endocrinol 2003, 176: 133-141.

63. Hinke SA, Gelling RW, Pederson RA, Manhart S, Nian C, Demuth HU, McIntosh CH. Dipeptidyl peptidase IV-resistant [D-Ala2]glucose-dependent insulinotropic polypeptide (GIP) improves glucose tolerance in normal and obese diabetic rats. Diabetes 2002, 51: 656-661

64. Irwin N, O'Harte FP, Gault VA, Green BD, Greer B, Harriott P, Bailey CJ, Flatt PR. GIP(Lys16PAL) and GIP(Lys37PAL): novel long-acting acylated analogues of glucose-dependent insulinotropic polypeptide with improved antidiabetic potential. J Med Chem 2006; 49: 1047-54.

65. Gault VA, Kerr BD, Irwin N, Flatt PR. C-terminal mini-PEGylation of glucose-dependent insulinotropic polypeptide exhibits metabolic stability and improved glucose homeostasis in dietary-induced diabetes. Biochem Pharmacol 2008; 75: 2325-33.

66. Kerr BD, Irwin N, O'Harte FP, Bailey CJ, Flatt PR, Gault VA. Fatty acid derivatised analogues of glucose-dependent insulinotropic polypeptide with improved antihyperglycaemic and insulinotropic properties. Biochem Pharmacol 2009; 78: 1008-16.

67. Martin CM, Irwin N, Flatt PR, Gault VA (2013) A novel acylated form of (d-Ala(2))GIP with improved antidiabetic potential, lacking effect on body fat stores. Biochim Biophys Acta 1830:3407–3413.

68. Flatt PR. Dorothy Hodgkin Lecture, 2008. Gastric inhibitory polypeptide (GIP) revisited: a new therapeutic target for obesity-diabetes? Diabetic Med 2008, 25:759–764

69. Irwin N, Flatt PR. Evidence for beneficial effects of compromised gastric inhibitory polypeptide action in obesity-related diabetes and possible therapeutic implications. Diabetologia 2009 ; 52:1724-31.

70. Hinke SA, Manhart S, Speck M, Pederson RA, Demuth HU, Mcintosh CHS. In depth analysis of the N-terminal bioactive domain of gastric inhibitory polypeptide. Life Sci 2004, 75: 1857–1870.

71. Hansen LS, Sparre-Ulrich AH, Christensen M, Knop FK, Hartmann B, Holst JJ, et al. N-terminally and C-terminally truncated forms of glucose-dependent insulinotropic polypeptide are high-affinity competitive antagonists of the human GIP receptor. Br J Pharmacol 2016, 173, 826–838.

72. Deacon CF. Circulation and degradation of GIP and GLP-1. Horm Metab Res 2004, 36: 761–765.

73. Tseng CC, Zhang XY, Wolfe MM. Effect of GIP and GLP-1 antagonists on insulin release in the rat. Am J Physiol 1999, 276: E1049–E1054.

74. Gelling RW, Coy DH, Pederson RA, Wheeler MB, Hinke S, Kwan T et al. GIP(6-30amide) contains the high affinity binding region of GIP and is a potent inhibitor of GIP1-42 action in vitro. Regul Pept 1997, 69: 151–154.

75. Hinke SA, Manhart S, Pamir N, Demuth HU, Gelling W, Pederson RA et al. Identification of a bioactive domain in the aminoterminus of glucose-dependent insulinotropic polypeptide (GIP). Biochim BiophysActa - Protein Struct Mol Enzymol 2001, 1547: 143–155.

76. Pathak V, Gault VA, Flatt PR, Irwin N. Antagonism of gastric inhibitory polypeptide (GIP) by palmitoylation of GIP analogues with N- and C-terminal modifications improves obesity and metabolic control in high fat fed mice. Mol Cell Endocrinol 2015, 401: 120–129.

77. Gasbjerg LS, Christensen MB, Hartmann B, Lanng AR, Sparre-Ulrich AH, Gabe MBN et al. GIP(3-30)NH2 is an efficacious GIP receptor antagonist in humans: a randomised, double-blinded, placebo-controlled, crossover study. Diabetologia 2018; 61:413–423.

78. Gasbjerg LS, Helsted MM, Hartmann B, Jensen MH, Gabe MBN, Sparre-Ulrich AH et al. Separate and combined glucometabolic effects of endogenous glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 in healthy individuals. Diabetes 2019; 68: 906–917

79 Piteau S, Olver A, Kim SJ, Winter K, Pospisilik JA, Lynn F, et al. Reversal of islet GIP receptor down-regulation and resistance to GIP by reducing hyperglycemia in the Zucker rat. Biochem Biophys Res Comm 2007, 362: 1007-12.

80. Hojberg PV, Vilsboll T, Rabol R, Knop FK, Bache M, Krarup T, et al. Four weeks of near-normalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. Diabetologia. 2009; 52: 199–207.

81. Christensen M, Vedtofte L, Holst JJ, Vilsboll T, Knop FK. Glucose-dependent insulinotropic polypeptide: a bifunctional glucose-dependent regulator of glucagon and insulin secretion in humans. Diabetes 2011, 60: 3103–3109.

82. Asmar M, Simonsen L, Arngrim N, Holst JJ, Dela F, Bulow J. Glucose-dependent insulinotropic polypeptide has impaired effect on abdominal, subcutaneous adipose tissue metabolism in obese subjects. Int J Obes 2014, 38: 259–265.

83. Asmar M, Asmar A, Simonsen L, Dela F, Holst JJ, Bülow J. GIP-induced vasodilation in human adipose tissue involves capillary recruitment. Endocr Connect 2019, 1. Epub ahead of print. EC-19-0144.R1.

84. Nissen A, Christensen M, Knop FK, Vilsbøll T, Holst JJ, Hartmann B. Glucose-dependent insulinotropic polypeptide inhibits bone resorption in humans. J Clin Endocr Metab 2014, 99: E2325–E2329.

85. Gaudin-Audrain C, Irwin N, Mansur S, Flatt PR, Thorens B, Baslé M et al. Glucose-dependent insulinotropic polypeptide receptor deficiency leads to modifications of trabecular bone volume and quality in mice. Bone 2013, 53: 221–230.

86. Mieczkowska A, Irwin N, Flatt PR, Chappard D, Mabilleau G. Glucose-dependent insulinotropic polypeptide (GIP) receptor deletion leads to reduced bone strength and quality. Bone 2013, 56: 337–342.

87. Mohammad S, Patel RT, Bruno J, Panhwar MS, Wen J, McGraw TE. A naturally occurring GIP receptor variant undergoes enhanced agonist-induced desensitization, which impairs GIP control of adipose insulin sensitivity. Mol Cell Biol 2014; 34: 3618-29.

88. Campbell JE, Ussher JR, Mulvihill EE, Kolic J, Baggio LL, Cao X et al. TCF1 links GIPR signaling to the control of beta cell function and survival. Nature Medicine 2016, 22, 84–90.

89. Groeneveld ON, Kappelle LJ, Biessels GJ. Potentials of incretin-based therapies in dementia and stroke in type 2 diabetes mellitus. J Diabetes Investig. 2016; 7: 5–16.

90. Gault VA, Kerr BD, Harriott P, Flatt PR. Administration of an acylated GLP-1 and GIP preparation provides added beneficial glucose-lowering and insulinotropic actions over single incretins in mice with type 2 diabetes and obesity. Clin Sci (Lond) 2011; 121: 107-17.

91. Finan B, Ma T, Ottaway N, Müller TD, Habegger KM, Heppner KM et al. Unimolecular dual incretins maximize metabolic benefits in rodents, monkeys, and humans. Science Translational Medicine 2013: 5, 209ra151.

92. Finan B, Müller TD, Clemmensen C, Perez-Tilve D, DiMarchi RD, Tschöp M. Reappraisal of GIP pharmacology for metabolic diseases. Trends in Molecular Medicine 2016, 22, 359-376.

93. Finan B, Yang B, Ottaway N, Smiley DL, Ma T, Clemmensen C et al. A rationally designed monomeric peptide triagonist corrects obesity and diabetes in rodents. Nature Medicine 2015, 21, 27–36.

94. Nørregaard PK, Deryabina MA, Tofteng Shelton P, Fog JU, Daugaard JR, Eriksson PO, et al. A novel GIP analogue, ZP4165, enhances glucagon-like peptide-1-induced body weight loss and improves glycaemic control in rodents. Diabetes Obes Metab 2018; 20: 60-68.

95. Pathak NM, Pathak V, Gault VA, McClean S, Irwin N, Flatt PR. Novel dual incretin agonist peptide with antidiabetic and neuroprotective potential. Biochem Pharmacol 2018; 155: 264-274.

96. Bergmann NC, Lund A, Gasbjerg LS, Meessen ECE, Andersen MM, Bergmann S, et al. Effects of combined GIP and GLP-1 infusion on energy intake, appetite and energy expenditure in overweight/obese individuals: a randomised, crossover study. Diabetologia 2019; 62: 665-675.

97. Tschöp MH, Finan B, Clemmensen C, Perez-Tilve D, Müller TD, DiMarchi RD. Unimolecular polypharmacy for treatment of diabetes and obesity. Cell Metabolism 2016, 24, 51-62.

98. Coskun T, Sloop KW, Loghin C, Alsina-Fernandez J, Urva S, Bokvist KB, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept. Molecular Metabolism 2018, 18, 3-14.

99. Frias JP, Nauck MA, Van J, Mark DO, Kutner E, Cui X et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. Lancet 2018, 392, 2180-2193

100. Portron A, Jadidi S, Sarkar N, DiMarchi R, Schmitt C. Pharmacodynamics, pharmacokinetics, safety and tolerability of the novel dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 agonist RG7697 after single subcutaneous administration in healthy subjects. Diabetes Obes Metab 2017; 19: 1446–53.

101. Schmitt C, Portron A, Jadidi S, Sarkar N, DiMarchi R. Pharmacodynamics, pharmacokinetics and safety of multiple ascending doses of the novel dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 agonist RG7697 in people with type 2 diabetes mellitus. Diabetes Obes Metab 2017; 19: 1436–45.

102. Frias JP, Bastyr EJ, Vignati L, Tschöp MH, Schmitt C, Owen K et al. The sustained effects of adual GIP/GLP-1 receptor agonist, NNC0090-2746, in patients with type 2 diabetes. Cell Metab 2017; 26: 343–52.

103. Brandt SJ, Götz A, .Tschöp MH, Müller TD. Gut hormone polyagonists for the treatment of type 2 diabetes. Peptides 2018, 100, 190-201.

104. Bhat VK, Kerr BD, Vasu S, Flatt PR, Gault VA. A DPP-IV-resistant triple-acting agonist of GIP, GLP-1 and glucagon receptors with potent glucose-lowering and insulinotropic actions in high-fat-fed mice. Diabetologia 2013, 56, 1417–1424.

105. Gault VA, Bhat VK, Irwin N, Flatt PR. A novel GLP-1/glucagon hybrid peptide with triple-acting agonist activity at GIP, GLP-1 and glucagon receptors and therapeutic potential in high-fat fed mice. J Biol Chem 2013, 288: 35581-91.

106. Lean, MEJ, Leslie WS, Barnes AC, Brosnahn N, Thom G, Combie L et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol 2019, 7, 344-55.

107. Bailey CJ. Glucose-lowering therapies in type 2 diabetes: Opportunities and challenges for peptides. Peptides 2018, 100, 9-17.

Legend to Figures

Figure 1.

Amino acid sequence of glucose-dependent insulinotropic peptide (gastric inhibitory peptide, GIP) showing functional properties and species differences. Structure-activity relationships of variant GIP molecules were assessed using an assay of cAMP production by Chinese hamster ovary (CHO) cells and monkey kidney (COS) cells transfected to express human GIP receptors [70, 71]. GIP(1-42) is the main active form of GIP, and GIP(1-30) is also active in the circulation. The N-terminal GIP(1-14) amino acids are essential for biological activity: the middle region (amino acids 19-30) affect receptor binding affinity and C-terminal amino acids (31-42) provide conformational advantage. GIP(1-42) is degraded by dipeptidyl peptidase-4 (DPP-4) to GIP(3-42), which can act as a competitive antagonist to GIP(1-42) at the GIP receptor. GIP variants with further deletions at the N-terminus can also act as antagonists at the GIP receptor: the antagonistic potency reduces with the number of deletions from the N-terminal sequence. The C-terminal region of GIP(1-42) reduces the competitive potency of GIP antagonists. There are small variations in the amino acid sequences of human, rat and mouse GIP molecules which do not alter the essential active N-terminal region but can alter biological activity between species.

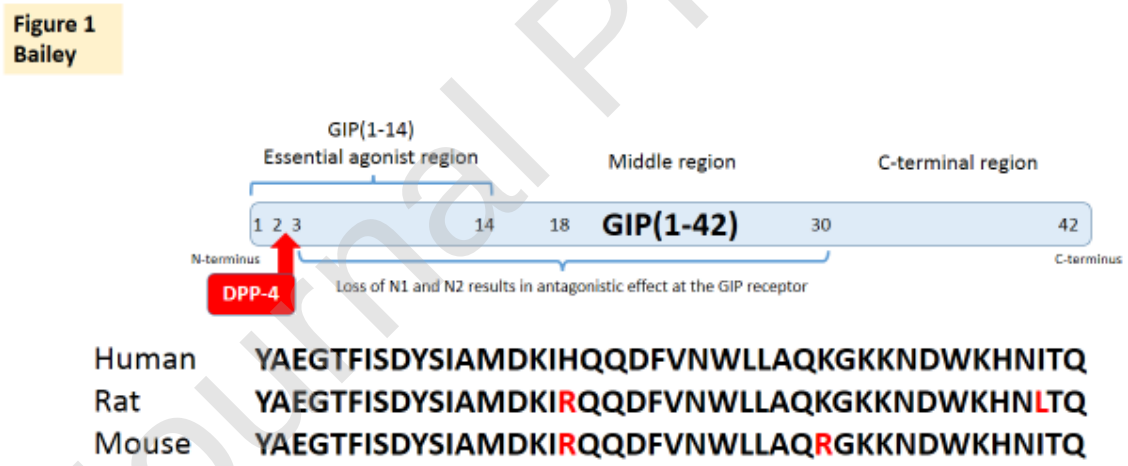

Figure 2

Amino acids sequences of glucose-dependent insulinotropic peptide (gastric inhibitory peptide, GIP), glucagon-like peptide-1 and glucagon compared with a dual GIP/GLP-1 receptor agonists and triple GIP/GLP-1/glucagon receptor agonists. Amino acids consistent with GIP are shown in black. X, aminoisobutyric acid. A, D-Ala2. [a] GIP/GLP-1 'twincretin' described by Finan et al [91]. [b] GIP/GLP-1 hybrid described by Pathak et al [95]. [c] GIP/GLP-1dual agonist tirzepatide also known as LY3298176 described by Coskun et al [98]. [d] Triagonist A decribed by Finan et al [93]. [e] Triagonist B ([DA2]GLP1/GcG) described by Gault et al [105].

Figure 2
Bailey

GIP, GLP-1 and glucagon

GIP	YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ
GLP-1	HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG
Glucagon	HSQGTFTSDYSKYLDSRRAQDFVQWLMNT

GIP/GLP-1 dual agonists

Twincretin[a]	YXEGTFTSNYSIYLNKQAAXEFVNWLLAGGPSSGAPPPSK
Hybrid[b]	YAEGTFISDYSIAMDYSSYLEGQAAKEFIAWLVKGKKNDWKHNITQGPSSGAPPPS
Tirzepatide[c]	YXEGTFTSDYSIXLDKIAQKAFVQWLIAGPSSGAPPPS-NH_2

GIP/GLP-1/glucagon triple agonist

Triagonist A[d]	HXQGTFTSDKSKYLDERAAQDFVQWLLDGGPSSGAPPPS-NH_2
Triagonist B[e]	YAEGTFISDYSKYLDSRRAQDFIAWLVKGR-NH_2

Table 1.

Glucoregulatory effects of gastro-intestinal and pancreatic peptides in clinical use or being investigated as templates to develop GIP-based therapeutic interventions for obese type 2 diabetes. Based on a recent review [107]. ↑, increase; ↓, decrease; ↔, no clear change; ?, uncertain; *, depends on pathophysiological circumstances; CCK, cholecystokinin; GIP, glucose-dependent insulinotropic peptide; GLP1, glucagon-like peptide 1; Oxynto, oxyntomodulin; PYY, peptide tyrosine tyrosine;

	HbA1c	Wt	Food intake	Energy expended	Insulin b-cell mass
GIP	↓	↑	**?**	↓	↑
GLP-1	↓	↓	↓	**?**	↑
Glucagon	↑	↓	↓	↑	↑
Insulin	↓	↑	↓	↓↔↑*	↔
PYY	↔	↓	↓	**?**	**?**
Oxynto	↓	↓	↓	↑	↑
Gastrin	↔	↔	↓	↔	↑
CCK	↔	↔	↓	↔	↔
Xenin	↔	↓	↓	**?**	↑