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Glucagon-based therapy for people with diabetes and obesity: What is the sweet spot?

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ABSTRACT

People with obesity and type 2 diabetes have a high prevalence of metabolic-associated steatotic liver disease, hyperlipidemia and cardiovascular disease. Glucagon increases hepatic glucose production; it also decreases hepatic fat accumulation, improves lipidemia and increases energy expenditure. Pharmaceutical strategies to antagonize the glucagon receptor improve glycemic outcomes in people with diabetes and obesity, but they increase hepatic steatosis and worsen dyslipidemia. Co-agonism of the glucagon and glucagon-like peptide-1 (GLP-1) receptors has emerged as a promising strategy to improve glycemia in people with diabetes and obesity. Addition of glucagon receptor agonism enhances weight loss, reduces liver fat and ameliorates dyslipidemia. Prior to clinical use, however, further studies are needed to investigate the safety and efficacy of glucagon and GLP-1 receptor co-agonists in people with diabetes and obesity and related conditions, with specific concerns regarding a higher prevalence of gastrointestinal side effects, loss of muscle mass and increases in heart rate. Furthermore, co-agonists with differing ratios of glucagon:GLP-1 receptor activity vary in their clinical effect; the optimum balance is yet to be identified.

1. Introduction

Obesity affects 14 % of adults globally [1] and diseases associated with high body mass index are responsible for nearly 5 million deaths annually [2]. Obesity and overweight lead to metabolic disturbances including insulin resistance and insufficient secretion, promoting glucose intolerance and the development of type 2 diabetes (T2D; [3]). Diabetes and obesity are also almost universally associated with ectopic fat deposition in the liver: this process is known as metabolic-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD; [4]). Of more concern is the development of steatohepatitis in around 1 in 3 people with overweight/obesity [5], which is known as metabolic-associated or steatohepatitis (MASH), formerly non-alcoholic steatohepatitis (NASH). People with MASH have a roughly 1 in 10 chance of developing cirrhosis and decompensated liver disease. People with obesity are prone to additional sequelae affecting almost all body systems and contributing to their disease burden [6]; these include hyperlipidemia and chronic kidney disease [7]. There is a huge unmet need for therapeutics to treat obesity and related conditions.

Glucagon was first discovered just over 100 years ago, as a pancreatic precipitate, distinct from insulin, which raised blood sugar in pancreatectomized dogs [8]. Its biology and role as a key hormone in glucose homeostasis have since been well-established [9]. Glucagon is a 29-amino acid polypeptide which is inherently unstable in aqueous solution, but has been formulated for different delivery systems including reconstitution and injection, pre-filled syringes and nasal spray [10]. It is widely used in clinical practice as a treatment for hypoglycemia [11].

Glucagon's other metabolic effects have recently become of interest to researchers seeking solutions for obesity and related conditions [12]. Notably, glucagon decreases liver fat via a direct action on hepatocytes: it decreases transcription of fatty acid synthesis genes and upregulates those governing fatty acid oxidation [13]. It also decreases plasma lipids including total cholesterol and triglycerides [14,15]. Acutely, glucagon increases energy expenditure [16], which could potentially contribute to body weight reduction. Other potentially positive actions of glucagon for people with diabetes and obesity include an increase in natriuresis [17]; and a direct effect on renal tubules to increase glomerular filtration and urea excretion, which can improve chronic kidney disease [18]. Conversely, actions of glucagon which may be less helpful for this cohort include enhanced hepatic uptake and catabolism of amino acids [13], which could lead to muscle mass loss and weakening [19]; and possible

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increases in heart rate and blood pressure, which could exacerbate risk of cardiovascular events [20].

The actions of glucagon are therefore potentially conflicting for people with obesity and T2D. One school of thought is that excessive glucagon activity is key to the hyperglycemia observed in T2D and thus suppression of glucagon activity could be a useful treatment for diabetes and obesity [21]. On the other hand, glucagon receptor (GCGR) agonism could decrease liver fat, reduce hyperlipidemia and assist in weight loss for this group. It is interesting to note that both agonism and antagonism of another incretin receptor, glucose-dependent insulinotropic peptide receptor (GIPR), can both decrease body weight and improve glucose homeostasis [22–24]. Though at first sight paradoxical, the concept of both up- and down-regulating actions of glucagon-related hormones for treatment of diabetes and obesity therefore has precedent.

It is notable that people with obesity, MASLD and T2D exhibit hyperglucagonemia [25,26]. They also have elevated circulating amino acids, which glucagon infusion fails to reduce, suggesting that they are resistant to the actions of glucagon, as glucagon stimulates hepatic uptake and catabolism of amino acids [27,28]. Intriguingly, surrogate markers of glucagon resistance (hyperglucagonemia with hyperaminoacidemia) are higher in people with T2D and MASLD than in weight-matched controls with T2D and without MASLD [29]. This raises the possibility that liver injury in diabetes and obesity drives hyperglucagonemia in people with MASLD, either directly or as part of a physiological compensatory response to counteract deleterious fat deposition in the liver and hyperlipidemia. This could then promote worsening of glucose control leading to the development or worsening of T2D in susceptible individuals. Surrogate markers of glucagon resistance improve following weight loss and improvement in MASLD (recently reviewed by the authors in [26]).

In this review we will summarize the findings of clinical trials which have investigated pharmacological GCGR manipulation in people with T2D (Fig. 1).

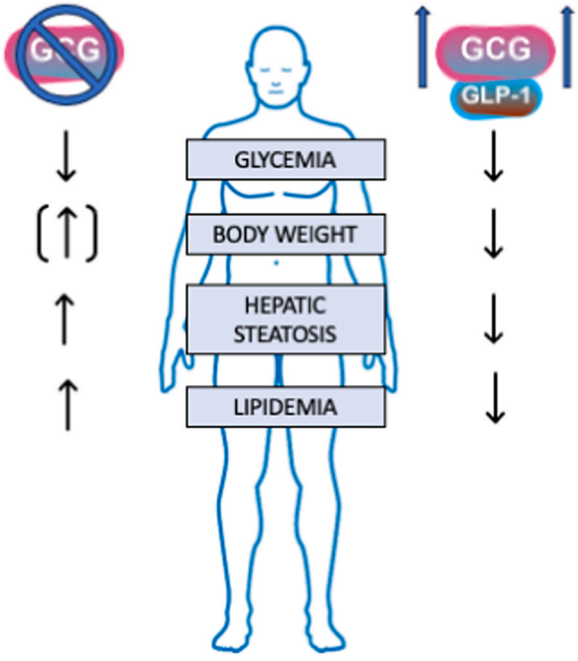

Fig. 1. Effects of blocking or increasing the actions of glucagon (as a co-agonist of glucagon and GLP-1 receptors) in people with obesity and T2D. GCG: glucagon. GLP-1: glucagon-like peptide 1.

2. Glucagon receptor antagonists for people with diabetes and obesity

The rationale for decreasing GCGR activity in T2D is clear. Genetic or pharmacological blockade of the GCGR in rodents is invariably associated with a reduction in fasting blood glucose (FBG) and improved glucose tolerance [30–32]. Administration of BAY 27–9955, a GCGR antagonist, attenuated the expected glucagon-induced increase in plasma glucose and hepatic glucose production in healthy volunteers [33]. Similarly, six weeks' treatment with ISIS 325568, a first-generation antisense oligonucleotide which decreases GCGR expression, attenuated plasma glucose area-under-curve (AUC) in response to a glucagon challenge [34].

Clinical trials investigating chronic treatment with drugs that block the activity of glucagon in people with T2D are summarized in Table 1. These are predominantly small-molecule GCGR antagonists that are given once daily [35–38], although other strategies include a second generation antisense oligonucleotide targeting hepatic expression of GCGR (IONIS-GCGR$_{Rx}$) which can be given weekly [39], or monoclonal antibodies to the GCGR (RN909), given monthly [40]. Studies have been performed in people with mild T2D with HbA1c in the region of 7.5–10.5 %, either in the absence of other medications or on a stable dose of metformin. Drugs reducing glucagon activity have been compared with placebo and/or metformin. Consistently GCGR antagonists are associated with improvement in glycemic markers including FBG, HbA1c and glucose AUC following a mixed meal [35–40]. These effects are not associated with an increased incidence of hypoglycemia. In studies lasting around 12–24 weeks, the magnitude of reduction in HbA1c is around 1–2 % and that of FBG 30–60 mg/dl, which would be considered by most practitioners to be clinically significant [41].

Blocking GCGR is, however, robustly associated with increases in serum transaminases, which is likely to reflect an increase in liver fat accumulation [35–38,40,42]. Morgan et al. directly demonstrated an increase in hepatic fat as measured by magnetic resonance spectroscopy in a study of 15 people taking IONIS-GCGR$_{Rx}$ [39]. These increases in transaminases appear to return to baseline on cessation of the drug [36, 38], but they nonetheless represent a major limitation to the use of GCGR antagonists in a population with a high prevalence of MASLD. Furthermore, many studies report worsening of hyperlipidemia [35,37, 42], related to glucagon's role in accelerating hepatic clearance of cholesterol [14]. Several studies demonstrate a small increase in body weight (most notably [35]), consistent with a reduction in glucagon signaling decreasing energy expenditure. Glucagon levels increase when GCGR activity is inhibited, likely via a decrease in hepatic amino acid catabolism and consequent increase in plasma amino acids stimulating pancreatic alpha cell secretion [43]. Since GLP-1 is processed from the same proglucagon peptide its levels also increase [32,36,39]. GLP-1 acts centrally to increase satiety; it also potentiates insulin secretion and thus could assist in the improvements in glycemia observed following glucagon receptor antagonism [44].

In mice, GCGR blockade or knockdown is associated with alpha-cell hyperplasia and gross pancreatic hypertrophy [31,45,46]. People with a congenital missense mutation of the GCGR also have alpha-cell hyperplasia with formation of glucagonomas [47]. The extent to which alpha cell hyperplasia might occur in people treated with glucagon receptor antagonists chronically is unknown. A study of a GCGR blocking monoclonal antibody REGN1193 in cynomolgus monkeys with diabetes demonstrated improvements in blood glucose without alpha-cell hyperplasia but the duration of this trial was only 8 weeks [31]. As well as alpha-cell mass, treatment with GCGR monoclonal antibodies in mouse models of diabetes increases beta-cell mass, which is likely due to alpha-to-beta-cell transdifferentiation [48]. The magnitude of this effect is dose dependent [49]. Increase in alpha-cell turnover, without alpha-cell hyperplasia, has also been observed in rodents treated with the peptide-based glucagon receptor antagonist desHis1Pro4Glu9-glucagon(Lys12PAL) [50]. At present, it is not known

Table 1
Clinical trials of glucagon receptor antagonists in people with T2D.

Name	Mode of action and mode of delivery	Cohort and duration	Compared with	Effects on glycemia^	Other effects
MK-0893 [35]	Small-molecule GCGR antagonist Oral, given once daily	342 with T2D 12 weeks	Metformin 1 g twice daily (MET), placebo (PBO)	↓ HbA1c (1.5 % versus 0.8 % MET vs increase of 0.5 % PBO) ↓ FPG (63 mg/dl vs 37 mg/dl MET vs 2 mg/dl PBO) No difference in hypoglycemia incidence	↑ LDL-C (15 mg/dl versus 1 mg/dl MET versus decrease of 3 mg/dl PBO) ↑ALT (31 % versus 0 % MET and 12 % PBO) ↑body weight (2.3 kg versus decrease of 1 kg MET and 0.9 kg PBO)
LY2409021 [36]	Small-molecule GCGR antagonist Oral, given once daily	254 with T2D and overweight/ obesity 24 weeks	PBO	↓HbA1c (0.92 % versus 0.15 % placebo) No difference in hypoglycemia incidence	↑serum transaminases ↑glucagon ↑GLP-1 No change in body weight
PF-06291874 [37,42]	Small-molecule GCGR antagonist Oral, given once daily	172 with T2D 28 days	PBO	Dose-dependent ↓glucose AUC following a mixed meal (approx. −25 %) ↓ FPG (57.2 mg/dL) No differences in hypoglycemia	Dose-dependent ↑glucagon AUC following a mixed meal (approx. 500 %) ↑serum transaminases ↑TC, LDL-C in the highest dose group (>10 %) Unrelated to dose: ↑body weight of around 1 kg
		206 with T2D on MET 12 weeks	PBO	Dose-dependent ↓ HbA1c (0.93 %) ↓ FPG (33.3 mg/dL)	Unrelated to dose: ↑serum transaminases (approx. 35–50 U/l) ↑ body weight <0.5 kg ↑LDL-C (<10 %) ↑blood pressure (systolic <2 mmHg)
RVT-1502 / LGD-6972 [38]	Small-molecule GCGR antagonist Oral, given once daily	166 with T2D and overweight/ obese on a stable dose of MET only 12 weeks	PBO	↓ HbA1c (-1.05 % relative to PBO) ↓ FPG (2.6 mmol/L relative to PBO) Mild hypoglycemia in 8 % of people on RVT-1502, none severe	Unrelated to dose: ↑ serum transaminases No significant differences to placebo in body weight, lipidemia changes
RN909 [40]	Human monoclonal antibody blocking GCGR Intravenous or sub-cutaneous injection, administered every 4 weeks	40 with T2D on stable MET 85 days	PBO	↓HbA1c (1.56 % versus 0.1 %) ↓glucose AUC after meal (27.9 % versus 3.0 %) No hypoglycemic events	No changes in total cholesterol or triglycerides ↑blood pressure ↑serum transaminases
IONIS-GCGR$_{Rx}$ [39]	Second-generation antisense oligonucleotide targeting GCGR Subcutaneous injection, administered weekly	T2D on stable MET 14 weeks 77 (for blood test outcomes) 15 (for hepatic lipid and glycogen as assessed by MRS)	PBO	↓HbA1c (2.0 % versus 0.3 %) No hypoglycemic events	↑serum transaminases ↑glucagon ↑GLP-1 ↑hepatic lipid content (4.2 % versus reduction of 2.7 % with PBO) Trend to ↑liver glycogen content (15.5 versus reduction by 20.2 mmol/L with PBO)

Where several doses were tested, mean result is quoted for the highest dose. Where manuscripts summarized the results of more than one study, the one with the longest duration is quoted. Hypoglycemic events refer to those that were severe or symptomatic. PBO: placebo; MET: metformin; FBG: fasting blood glucose; T2D: type 2 diabetes; GCGR: glucagon receptor; GLP-1: glucagon-like peptide 1; MRS: magnetic resonance spectroscopy.
^change from baseline

whether chronic treatment with GCGR antagonists increases functional beta-cell mass in people with T2D.

3. Co-agonism of the glucagon and GLP-1 receptors for people with diabetes and obesity

In recent years several unimolecular co-agonists of the GCGR and GLP-1R have been developed, harnessing the beneficial metabolic actions of glucagon for people with obesity related disease. This approach has been underpinned by studies in which glucagon and GLP-1 have been co-infused, resulting in an increase in energy expenditure when compared to GLP-1 infusion alone and attenuation of hyperglycemia when compared to glucagon alone [51,52]. In fact, the endogenous hormone oxyntomodulin (formed by alternative processing of the proglucagon peptide) is a co-agonist peptide that binds to and activates both the GCGR and GLP-1R, and in preclinical studies is associated with improved glucose tolerance, reduced food intake and increased energy expenditure [53]. The additional effect on energy expenditure, as noted, would advantageously improve weight loss.

Another strategy to improve efficacy is to add in another receptor activity by developing unimolecular tri-agonists of GCGR, GLP-1R and the glucose-dependent insulinotropic peptide receptor (GIPR). GLP-1 and GIP are both incretin hormones which are secreted from the gut in response to a meal and promote pancreatic insulin secretion in healthy volunteers, thus attenuating post-prandial glycemia [54]. As this review is focused on glucagon-based treatment, for further details on the ins and outs of adding on GIPR agonism vs antagonism to GLP-1R agonism for therapy, we refer the interested reader to our separate and recent review on the subject [24]. Dual agonism of GIPR and GLP-1R has emerged as a viable method for treatment of diabetes and obesity, culminating in the marketing of the dual GLP-1R/GIPR agonist tirzepatide which is clinically superior to the GLP-1 monoagonist semaglutide for glycemic improvement and weight loss in people with T2D [55], and is effective for treatment of obesity without T2D [56]. Following

logically on from this concept, triagonists such as retatrutide, SAR441255 and efocipegtrutide have been developed and these are discussed below.

In Table 2 and Supplementary Table 1, co-agonists have been organized with respect to their relative potency at the GCGR and GLP-1R. It should be noted that although most studies have assessed potency by measuring cAMP production in cell systems containing the human or murine receptors, there are additional downstream signaling pathways which also contribute to metabolic effects of these peptides. For example, glucagon receptor activation also activates phospholipase C (PKC)/protein kinase A (PKA) signaling, causing release of intracellular calcium independent of cAMP [57]. Changes in calcium flux may contribute to triglyceride lipolysis and gluconeogenesis [58]. Additionally, GCGR internalization, downregulation and desensitization via ß-arrestin recruitment crucially influences receptor activity [59]. The roles of ß-arrestin recruitment by GCGR with respect to clinical effects

Table 2
Clinical trials of glucagon receptor co-agonists in people with T2D.

	Dosing, comparators and duration	Body weight	Glucose tolerance	Other findings	Tolerance and safety	Human cAMP output ratio GLP-1R: GCGR: GIPR *	Other indicator of relative GLP-1R: GCGR: GIPR activity^
GLP-1R and GCGR co-agonists with balances favoring GLP-1R							
SAR425899 [63,64]	Daily. PBO, over 28 days	↓5.5 kg	↓HbA1c (0.59 % versus increase of 0.06 % PBO) ↓FPG (3.04 mmol/L versus 1.24 PBO)	Slightly greater improvements in lipidemia in treated group when compared to PBO ↑ heart rate 4 bpm (no change in PBO group)	Development discontinued due to high rate of GI AEs	5:1 [63]	Receptor occupancy using PET of liver and pancreas. GLP-1R occupancy: 50 %. GCGR occupancy: negligible, suggesting that it is functionally a GLP-1R monoagonist [64]
Cotadutide [65–68]	Daily. Liraglutide 1.8 mg, over 54 weeks. PBO, over 41 or 49 days	↓5 % vs ↓3.3 % liraglutide over 54 weeks	↓HbA1c (1.19 % versus 1.17 % liraglutide) over 54 weeks	↓plasma triglycerides (9.8 mg/dl versus 1.3 mg/dl liraglutide) over 54 weeks ↓AST (9 U/l versus increase of 0.35 with liraglutide) over 54 weeks ↓liver fat on MRI-PDFF (6 % versus 3 % PBO) over 41 days ↑heart rate by 7 bpm over 49 days	Mild GI AEs Hypoglycemia 14 % versus 5 % PBO	1.02: 0.19	Mouse cAMP output ratio 2.88: 0.71
GLP-1R and GCGR co-agonists with balanced activity							
Mazdutide [69,70]	Once weekly, Dulaglutide 1.5 mg and PBO, over 12 weeks	↓5.4 % versus ↓0.9 % dulaglutide and ↓1.1 % PBO	↓HbA1c (1.66 % versus 1.98 % dulaglutide and 0.87 % for PBO) ↓FBG (4.07 mmol/L versus 3.85 mmol/L dulaglutide and 2.52 PBO)	↑heart rate (<15 bpm versus <10 bpm with dulaglutide)	Mild GI AEs comparable between groups	-	Binding affinity (Ki) 17.7 nM at GCGR versus 28.6 nM at GLP-1R i.e. 1:1.6 in favor of GCGR
JNJ-64565111 [71,72]	Once weekly, PBO, over 12 weeks	↓7.9 % versus ↓0.7 % placebo	No significant improvement in HbA1c or FPG	Greater improvement in plasma triglycerides and total cholesterol than PBO	High incidence of mild/ moderate GI side effects	-	'Comparable potency'
GLP-1R, GCGR and GIPR tri-agonist with balanced activity at GLP-1R and GCGR							
Retatrutide [73,74]	Once weekly, Dulaglutide 1.5 mg and placebo, over 36 weeks	↓17.2 kg versus1.97 kg dulaglutide 1.5 mg and 3.28 kg PBO	↓HbA1c (2.02 % versus 1.41 % dulaglutide and increase of 0.01 % PBO) over 24 weeks ↓FBG (3.77 mmol/L versus 1.53 mmol/L dulaglutide and 0.97 mmol/L PBO over 36 weeks)	Significant improvement in hyperlipidemia including ↓plasma total cholesterol (16.7 % versus 0.93 % dulaglutide and 2.23 % PBO) ↓systolic blood pressure (9 mmHg versus 1.5 mmHg dulaglutide) ↑heart rate (4.34 bpm versus 1.76 dulaglutide and decrease of 3.16 bpm with PBO)	High incidence of mild/moderate GI side effects (79 % participants versus 67 % dulaglutide and 62 % PBO)	40:34:950	-

Where several doses were tested, mean result is quoted for the highest dose. Where the results of more than one study is available, results from the one with the longest duration are given.
*EC_{50} native ligand/co-agonist for cAMP production × 100 % at the respective human receptor; in some cases this has been calculated from the provided data.
^where receptor activity was measured using a different method to cAMP production at the human receptor, this has been described and provided. PBO: placebo; FBG: fasting blood glucose; T2D: type 2 diabetes; GCGR: glucagon receptor; GLP-1: glucagon-like peptide-1; bpm: beats per minute; GI: gastrointestinal; AE: adverse effects; MRI-PDFF: magnetic resonance imaging-proton density fat fraction; PET: positron emission tomography.

and how we can exploit 'biased agonism' with agonists that reduce ß-arrestin recruitment are yet to be explored. The relative potency of individual co-agonists with respect to the native ligand for these measures may differ from cAMP measures. Furthermore, effectively titrating relative efficacy at the GCGR, GLP-1R ± GIPR using pre-clinical models remains a huge challenge for translational programs; for example, for some co-agonists the balance of receptor affinities differs dramatically between mice and humans [60]. Even in cases where balance between receptor affinities is well conserved between species, the clinical effects may differ, as in the case of NN-1177 which is associated with improvement in glucose tolerance in mice and worsening of glucose tolerance in rats [61]. The latter effect proved to be dominant in the Phase 1 trials, an important factor in abandoning development of NN-1177 [62].

3.1. Dual agonists with balances favoring GLP-1R activity

3.1.1. SAR425899

SAR425899 (Table 2) was developed as a peptidic dual agonist with a 5:1 balance in favor of GLP-1R in in vitro studies. Despite its dual agonist activity in vitro, functionally SAR425899 is a GLP-1R agonist with negligible GCGR activity. This is evidenced by a study estimating receptor occupancy of SAR425899 using positron emission tomography of the liver and pancreas, which demonstrated robust occupancy of GLP-1R but no evidence of peptide occupancy at the GCGR [64]. Two placebo-controlled RCTs, involving people with and without T2D, demonstrated reductions in body weight at the highest doses over 21–28 days of around 5 kg in both groups [63]. Weight was rapidly regained on cessation of the drug. In people with T2D, improvements in fasting plasma glucose and HbA1c were also seen [63]. In a separate study, 28 days treatment was associated with improvements in calculated indices of beta-cell function and glucose absorption in people with T2D [75]. However, participants taking SAR425899 reported a high rate of adverse events (AE), most commonly gastrointestinal. Following a single dose, 16 of 24 participants experienced one AE, including vomiting and dizziness [63]. In another study, 10 of 13 people experienced an AE, of which 6 discontinued treatment due to the AE [64]. Treatment for 3–4 weeks was associated with an increase in average heart rate of around 4–5 beats per minute [63]. Development of this peptide has been discontinued due to its AE profile.

3.1.2. Cotadutide/MEDI0382

Cotadutide (Table 2) is a peptidic dual agonist which has a 5-fold balance favoring GLP-1R, as assessed by cAMP output assays at both human and mouse receptors, and is administered once daily. There have been several trials of this medication in people with overweight/obesity and T2D. At the highest dose of 300 mg/day, cotadutide has similar effects on HbA1c as liraglutide 1.8 mg (reduction of around 1.2 % at 54 weeks). At this dose, subjects using cotadutide experienced around 5 % reduction in body weight which plateaued after 14 weeks of treatment and persisted to 54 weeks, compared to around 3 % in people on liraglutide [66]. In a separate study of Asian subjects with or without T2D, a similar weight loss was seen over 48 days [76]. When assessed with oral glucose tolerance test (OGTT), people with T2D treated for 32 or 49 days with cotadutide exhibited a reduction in glucose AUC accompanied by an increase in insulin AUC and prolonged gastric emptying [68,77].

Cotadutide at the highest dose led to improvements in transaminases and other biomarkers of MASLD, which were not seen following treatment with liraglutide [66]. In a separate study of people with T2D and obesity, treatment with 200 mg cotadutide over 41 days lead to greater reduction in liver fat than placebo as assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF); the reduction was correlated with reduction in body weight [67]. In subjects with overweight/obesity, T2D and chronic kidney disease, cotadutide over 32 days was associated with a numerical reduction in urinary albumin-to-creatinine ratio, with no difference in glomerular filtration rate [68].

Gastrointestinal AE are seen at a greater rate in people treated with cotadutide than liraglutide or placebo [66,68,78]; side effects tend to be mild and led to study discontinuation in 3–12 % [68,77,78]. Clinically significant hypoglycemia (<3 mmol/L) was seen in 14 % versus 5 % in placebo, with no serious AEs due to hypoglycemia [68]. Over 49 days an increase in pulse rate of 7 bpm was noted [77]; in another study over 32 days an increase of 14 bpm was noted [68]. Cotadutide is also no longer under development, with the manufacturer stating that they intend to focus on development of an alternative co-agonist which requires weekly administration [79].

3.1.3. Survodutide/BI 456906

Similarly to cotadutide, survodutide (Supplementary Table 1) is a peptidic dual agonist with a receptor activity balance tilted towards GLP-1R (around 5-fold), and designed with extended half-life making it suitable for once-or twice-weekly administration [80]. In volunteers without T2D, maximum placebo-corrected body weight decrease was 13.8 % at week 16 in one trial [81] and 12.4 % in another [82]. As with cotadutide, it appears that weight loss plateaus after 3 months or so, as a separate study reported a comparable body weight reduction of 14.9 % over 46 weeks in volunteers with overweight or obesity at the same maximum dose of 4.8 mg [83]. Survodutide is associated with a high rate of gastrointestinal AEs which are dose-dependent, in particular nausea, vomiting and decreased appetite (100 % versus 44 % in the placebo group in one study [82], 90 % versus 75 % taking placebo in another [83]). 7–26 % of participants discontinued treatment due to AEs [81–83]. A trial of survodutide in people with MASH has been reported in a press release to improve MASH and liver fibrosis on liver biopsies in up to 83 % given survodutide for 48 weeks versus 18 % given placebo [84]. Survodutide has yet to be investigated in people with T2D.

3.1.4. NN9204-1177/NN-1177

NN9204–1177 (or NN-1177: Supplementary Table 1) is a peptidic dual agonist with a balance of two to three-fold preference for GLP-1R, as assessed by cAMP assays at both human and mouse receptors [61]. It has been investigated in placebo-controlled sequential ascending dose studies in adults with overweight/obesity. The maximal placebo-adjusted body weight reduction was 12.6 % over 85 days; weight was regained on cessation of the drug. Although there were no clear dose-dependent changes in fasting plasma glucose nor HbA1c, the highest doses were associated with an increased AUC for glucose and insulin following an OGTT, indicating decreased glucose tolerance and potentially increased insulin resistance [62]. There was a high rate of AE (100 % in the highest doses tested compared to 70 % in placebo) – in one-third of people these led to premature discontinuation of the trial [62]. Gastrointestinal AE particularly nausea and vomiting were the most frequently reported. In the single-dose trial, 24 hours post-dosing, heart rate increased by up to 22 bpm; in the multiple-ascending dose study, after 85 days of treatment mean heart rate increase was up to 15 bpm. These changes were reversible within 30 days of discontinuing the drug. QT interval prolongation was also observed. The trial was stopped early due to safety concerns regarding the tachycardia and the two highest planned doses were not tested. This medication has not been trialed in people with T2D and overall development of this drug has been discontinued.

3.2. Dual or triple agonists with balanced activity at GLP-1R and GCGR

3.2.1. Mazdutide/IBI362/LY3305677

Mazdutide (Table 2) is a dual agonist with balanced activity at the GLP-1R and GCGR [69]. In people with overweight or obesity (BMI >24 kg/m^2) participants taking mazdutide lost up to 9.5 % body weight over 16 weeks (versus 3.3 % for placebo) [85]. In people with T2D inadequately controlled on diet or metformin (BMI 20–35 kg/m^2), treatment over 12 weeks led to a reduction in fasting glucose and HbA1c

which was comparable with dulaglutide 1.5 mg. Weight loss was however greater in the mazdutide group, with people losing around 5 % body weight compared to 1 % for people on dulaglutide [70]. Gastrointestinal side effect rates (diarrhea for around one-third of people, nausea for 16 %) were comparable in people on mazdutide and dulaglutide. Heart rate increases were seen in all treatment groups (change from baseline of 10–15 bpm) [70].

3.2.2. Efinopegdutide/JNJ-64565111/MK-6024

Efinopegdutide (Table 2) is a dual agonist peptide which is chemically conjugated to a human IgG4 fragment, making it suitable for once weekly administration. It is described as stimulating both GCGR and GLP-1R receptors with 'comparable potency' [71]. In a Phase 2 RCT of people with obesity (mean BMI 40 kg/m^2) and without diabetes, efinopegdutide over 26 weeks led to dose-dependent weight loss which was greater than liraglutide 3.0 mg once daily (10 % at the highest dose of 10 mg weekly compared to 5.8 %) [71]. There was a very high rate of treatment-emergent adverse effects (84 % in the highest dose compared to 61 % in the liraglutide group). These were predominantly nausea and vomiting in all groups and led to treatment discontinuation in 32 % versus 17 %. In people with T2D, despite efinopegdutide over 12 weeks giving an 8 % weight loss, there were no improvements in HbA1c or fasting plasma glucose when compared to placebo [72].

In a further RCT, efinopegdutide (up to 10 mg/week) was compared to semaglutide (up to 1 mg/week) in 145 people with overweight/obesity and liver fat >10 % as assessed by MRI-PDFF [86]. 33 % of included people had T2D. Treatment for 24 weeks led to superior reduction of liver fat in the efinopegdutide group (reduction from baseline of 73 % versus 42 %, $p<0.001$). This occurred alongside comparable weight loss in the efinopegdutide group (total % body weight loss at 24 weeks, 8.5 % versus 7.1 %) and improvements in lipidemia (total cholesterol at 24 weeks 4.4 mmol/L versus 4.7 mmol/L). Again, efinopegdutide was associated with slightly higher incidences of AE (88.9 % versus 72.6 %) which were predominantly gastrointestinal, with higher incidence of abdominal pain and constipation than semaglutide. People on efinopegdutide also experienced a greater increase in mean heart rate and greater reduction in blood pressure, without any related AE.

3.2.3. Retatrutide/LY3437943

Retatrutide (Table 2) is a unimolecular peptide agonist of the GLP1-R, GIPR and GCGR. At the human receptors, it exhibits balanced potency (assessed using cAMP assays) when compared to the native ligands for GLP-1R and GCGR, with 9-fold greater potency for GIPR than GIP [74]. In mice with diet-induced obesity, retatrutide given over 21 days decreases body weight and liver triglyceride, decreases fasting blood glucose and insulin, and increases ratio of lean to fat mass [74]. This is associated with a dramatic decrease in food intake, which does however normalize at around day 16. Whereas mice treated with retatrutide maintained their pre-treatment energy expenditure, a calorie-intake matched group decreased their energy expenditure substantially. Co-administration of a GCGR antagonist did not change the reduction in calorie intake but did block the effects on energy expenditure.

Retatrutide has been investigated in two recent randomized controlled trials where it was given as a once weekly injection. In 331 adults with obesity (mean BMI 37 kg/m^2) without T2D (approximately one-third had pre-diabetes), treatment led to substantial dose-dependent weight loss: the top dose of 12-mg was associated with a mean of 24 % weight loss over 48 weeks (placebo 2.1 %) [87]. A separate analysis of a subset of participants with MASLD demonstrated significantly greater reductions in liver fat content than placebo, in the region of 90 % reduction for people on the highest dose (data not published yet; [88]). A second trial looked at volunteers with T2D and overweight/obesity, with HbA1c between 7 % and 10.5 % on diet or metformin alone. After 24 weeks of treatment, mean reduction in HbA1c was 2.02 % for the highest dose of 12 mg group, which was significantly greater than both placebo and 1.5 mg dulaglutide [73]. This was associated with weight loss (17 kg over 36 weeks) and significant improvements in hyperlipidemia. Side effects were mostly gastrointestinal, including nausea, vomiting and change in bowel habit [73,87], and were dose dependent, occurring in 13 % of people with T2D on 0.5 mg and 50 % in people on 12 mg, compared with 35 % of participants in the dulaglutide group. A rise in heart rate was also noted, of around 4 beats per minute at 36 weeks for people on 12 mg; this was statistically different to placebo, but not to 1.5 mg dulaglutide. In RCTs of retatrutide no participant suffered from severe hypoglycemia (glucose <54 mg/dl or symptoms requiring treatment).

3.2.4. SAR441255

SAR441255 (Supplementary Table 1) is another peptide triagonist with comparable potency at GLP-1R, GIPR and GCGR. Unlike SAR425899, in vivo receptor occupancy data from PET studies do show that SAR441255 binds and occupies both GLP-1R and GCGR, favoring GLP-1R by 2:1 over GCGR (GIPR occupancy was not assessed) [89]. Chronic treatment with SAR441255 substantially reduces body weight in obese mice and cynomolgus monkeys. The compound has been tested in a Phase 1 single-dose trial in healthy volunteers [89]. Interestingly, fasting glucose fell to a nadir of around 3.5 mmol/L at 1 hour post-administration, returning to normal by 3 hours, during which no people suffered symptoms. After a mixed meal tolerance test, pre-treatment with SAR441255 was associated with an attenuation of rise in glucose, insulin and C peptide. The authors proposed that the attenuation of insulin and C peptide were due to a slowing in gastric emptying, which is a known effect of GLP-1R agonism. SAR441255 is not currently under development.

3.3. Triple agonists with balances favoring GCGR

3.3.1. Efocipegtrutide/HM15211

Efocipegtrutide (Supplementary Table 1) is a triple agonist GLP-1R/GCGR/GIPR peptide chemically conjugated to a human IgG4 fragment, thus increasing its half-life and making it suitable for once weekly administration. The authors describe it as having a 'high glucagon activity ratio' [90]. In obese mice, HM15211 reduces body weight to a greater degree than liraglutide, and increases energy expenditure. In mouse models of MASH, chronic treatment with efocipegtrutide reduces liver fat and improves MASLD/NAFLD activity score [90,91]. In non-diabetic volunteers with hepatic steatosis as assessed by MRI-PDFF, an ascending dose Phase 1b trial demonstrated that liver fat was reduced in a dose dependent way, with 80 % reduction over 8 weeks in the top dose group. This was associated with around 5 % weight loss. Two volunteers developed hyperglycemia, which resolved with discontinuation [92]. Results of a phase 2 52-week study of people with biopsy-confirmed MASH are awaited [93].

4. Promises and potential pitfalls of GCGR and GLP-1R co-agonism

The addition of GCGR agonism to GLP-1R agonism increases weight loss in people with diabetes and obesity. When compared to GLP-1R monoagonists, co-agonists which are heavily tipped in favor of GLP-1R activation increase weight loss to a small degree [66], with greater effects seen with co-agonists that are balanced at the two receptors [70]. Retatrutide has particularly impressive weight loss effects which may be attributable to its additional incorporation of GIPR agonism [73]. Weight regain occurs on cessation of co-agonists [62,63], as it does following cessation of GLP-1R monoagonists [94].

Inclusion of even a small amount of GCGR agonism is likely to improve hepatic steatosis and hyperlipidemia compared to GLP-1R monoagonism in people with diabetes and obesity, even where weight loss is comparable [66]. This is possibly an important added benefit from the inclusion of GCGR agonism, since GLP-1R monoagonists are

associated with moderate improvement in MASH but minimal improvement of liver fibrosis [95,96]. There are early suggestions that incorporation of glucagon agonism may be very helpful for liver outcomes in people with obesity and MASLD [67,84,88]; more studies are needed to investigate the clinical impact on MASLD/MASH in people with obesity and T2D.

The addition of GCGR to GLP-1R agonism does not worsen glycemia in comparative trials performed to date [66,70,73]; there is some evidence, however, that compounds with high GCGR activity may not improve measures of diabetes and could even lead to hyperglycemia [72,92]. A careful balance of receptor activities is required, but pre-clinical development to get this balance right can be tricky, as illustrated by the case of NN-1177 [61]. Nevertheless, if robust weight Ioss is obtained with chronic treatment, this may be enough to ensure that people with T2D benefit from improvements in glycemia when GCGR is added to GLP-1R agonism.

Gastrointestinal AEs are common with this class of medication, as they are with all GLP-1R agonists [97]. Prevalence of AEs is dose-dependent but not clearly related to relative potency at the two receptors. There is evidence that the medications become more tolerable over time; for example, with cotadutide the gastrointestinal adverse event rate fell over time on treatment [66]. As with GLP-1R monoagonists, the use of a step-wise escalation in dose mitigates symptoms to some extent [97]. Interestingly GIPR agonism has been demonstrated to attenuate GLP-1R agonist-induced nausea and vomiting in rodents [98]; potentially tri-agonists that incorporate effects at GLP-1R, GCGR and GIPR could have a favorable side-effect profile but the optimum balance will need to be established.

People with T2D tend to be sarcopenic [99], and further reductions in muscle mass are problematic. GCGR agonism does trigger catabolism and consequent reductions in plasma amino acids, a phenomenon which is evident in the clinical trials of cotadutide [77] and NN-1177 [62]. As noted in our introduction, in pre-clinical models, chronic GCGR agonism and hypoaminoacidemia is associated with lean mass loss and functional weakening of muscle strength [19]. Small studies suggest that GLP-1R monoagonists such as semaglutide may disproportionately reduce fat mass with a relative preservation of muscle mass and strength [100]. The question as to whether chronic co-agonism of GLP-1R and GCGR may cause significant muscle mass and strength reductions remains open.

Heart rate increases are commonly reported with GLP-1R/GCGR co-agonists [64,70,77], and are likely to be an 'on-target' effect since GLP-1 is positively chronotropic [101]. Although glucagon is positively chronotropic and inotropic in humans and has been used for treatment of beta-blocker overdose [102], there is some controversy as to whether glucagon has direct myocardial stimulatory effects, and whether glucagon receptors are expressed in the human heart [103]. Comparative studies so far suggest that the increase in heart rate with GLP-1R/GCGR co-agonists is similar in magnitude to that observed with GLP-1R monoagonism and also that heart rate may normalize to some extent with chronic treatment [70]. On the other hand, NN-1177 caused an increase in heart rate by 5–22 bpm (markedly higher than with GLP-1R monoagonists), and this was cited as an unacceptable safety concern [62]. It should be noted that acute heart rate increases recorded in clinical trials may not necessarily translate to actual adverse cardiovascular effects in Phase 3 and 4 trials. In the LEADER randomized-controlled trial of liraglutide versus placebo [104] and the SUSTAIN-6 RCT of semaglutide versus placebo [105], both conducted in people with T2D, both agents increased heart rate compared to placebo (3 bpm over 36 months; 2 bpm over 104 weeks respectively). Despite this, both agents improved cardiovascular outcomes, reducing deaths from cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke. This can be attributed to weight loss-dependent improvements in cardiovascular risk factors, including reduction in systolic blood pressure and improvement in hyperlipidemia and glycemia. GLP-1R agonists may also have weight loss-independent anti-thrombotic and anti-inflammatory effects in vascular endothelial and smooth muscle cells [106]. Long-term trials of cardiovascular outcomes will be required to establish the cardiovascular safety of glucagon co-agonists in people with obesity and T2D.

5. Conclusion

Antagonists of the GCGR are associated with robust improvements in measures of glycemic control in people with T2D. These drugs are, however, limited by their tendency to increase liver fat and worsen hyperlipidemia. Since most people with diabetes and obesity suffer from MASLD and dyslipidemia, antagonizing GCGR may not ultimately prove helpful. GCGR agonists, when combined with agonist activity at GLP-1R ± GIPR, are also associated with improvements in blood glucose in people with T2D. This is at least partially secondary to weight loss, which appears to be greater in peptides with greater relative GCGR efficacy. Additionally, current data would support the view that GCGR/GLP-1R co-agonists can improve liver fat and dyslipidemia in people with diabetes and obesity. The main limitation of these drugs is their gastrointestinal AE profile which has led to several of these medications halting development after early-phase clinical trials. Reassuringly, most people eventually tolerate the medications, and the severity of the AE can be attenuated by a gradual titration to full treatment dose. As with bariatric surgery, these medications should be viewed as an adjunct to lifestyle intervention (diet and exercise), as this will promote optimum and sustained health benefits, whilst reducing the chance of side-effects. In the future, there is potential for rational design and prescription of co-agonists for different clinical requirements: for example, utilizing drugs with activity balances favoring GCGR agonism in people with MASLD but who are not diabetic. This concept will need to be underpinned by continued research into the actions of glucagon in health and in people with varying degrees of overweight, obesity and metabolic-associated disease.

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Emma Rose McGlone: Writing – review & editing, Writing – original draft, Conceptualization. **Tricia M.M. Tan:** Writing – review & editing, Conceptualization.

Data availability

No data was used for the research described in the article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.peptides.2024.171219.

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