Combination gut hormones: prospects and questions for the future of obesity and diabetes therapy

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Abstract

Obesity represents an important public health challenge for the 21st century: globalised, highly prevalent and increasingly common with time, this condition is likely to reverse some of the hard-won gains in mortality accomplished in previous centuries. In the search for safe and effective therapies for obesity and its companion, type 2 diabetes mellitus (T2D), the gut hormone glucagon-like peptide-1 (GLP-1) has emerged as a forerunner and analogues thereof are now widely used in treatment of obesity and T2D, bringing proven benefits in improving glycaemia and weight loss, and, notably, cardiovascular outcomes. However, GLP-1 alone is subject to limitations in terms of efficacy; as a result, investigators are evaluating other gut hormones such as glucose-dependent insulinotropic peptide (GIP), glucagon and peptide YY (PYY) as possible partner hormones that may complement and enhance GLP-1's therapeutic effects. Such combination gut hormone therapies are in pharmaceutical development at present and are likely to make it to market within the next few years. This review examines the physiological basis for combination gut hormone therapy and presents the latest clinical results that underpin the excitement around these treatments. We also pose, however, some hard questions for the field which need to be answered before the full benefit of such treatments can be realised.

Obesity affects approximately 13% of the world's adult population with 39% being overweight (World Health Organisation, 2020). It is a multi-systemic disease state with serious co-morbidities that include cardiovascular disease, type 2 diabetes (T2D), hypertension, hyperlipidaemia, obstructive sleep apnoea, subfertility, cancers (breast, ovary, prostate, liver, endometrium, colon), and fatty liver disease/steatohepatitis leading to cirrhosis and liver failure. Key drivers of this tidal wave of obesity include poor nutrition from highly processed foods tuned to appeal to our hedonic responses, reduced or no opportunities for physical activity imposed by the physical environment and lifestyle choices, genetic factors which play a role in determining susceptibility to obesity and its complications, epigenetic factors arising from prenatal exposure to obesogenic influences and the less well understood phenomenon of microbiotal alteration leading to increased absorption of energy from food and a pro-inflammatory milieu driving the metabolic imbalances and deleterious consequences of obesity (De Lorenzo et al., 2020).

Much time and money have been spent on finding effective, safe, sustainable and cost-effective treatments for obesity and its cohort T2D. Lifestyle changes focusing on weight loss via calorie restriction, even despite modest weight losses, are overall effective in reducing mortality (Ma et al., 2017) and are judged cost-effective (Avenell et al., 2018). Pharmacotherapy utilising a variety of approaches such as pancreatic lipase inhibition (orlistat), cannabinoid receptor antagonism (rimonabant), 5-HT receptor activation (fenfluramine, sibutramine, lorcaserin), sympathetic nervous system activation (phentermine, sibutramine), combined activation of appetite-regulating pro-opiomelanocortin neurones (bupropion/naltrexone), and MetAP2 inhibition (beloranib) have been modestly effective in reducing weight but have been beset by adverse effects (Khera et al., 2016) which has led to the withdrawal of most of these treatments from development or the market. Bariatric surgery, for example Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy, has emerged over the past 4 decades as the most effective treatment for obesity, with documented long-term benefits in reducing mortality (Sjöström, 2013). Moreover, the prospect of enforcing the remission of obesity-associated T2D with surgery (Schauer et al., 2017), has led to recommendations that this

modality is considered for this condition (Rubino et al., 2016). However, the scalability of bariatric surgery is limited by the number of specialist surgeons/facilities for this surgery, the fact that some surgical candidates may not be fit enough to undertake surgery and the fact that many people remain apprehensive about taking up this option. Moreover, even though perioperative mortality is low, postoperative complications such as post-bariatric hypoglycaemia (Tharakan et al., 2017) can be extremely troublesome. Lastly, bariatric surgical procedures are 'one size fits all', where patients undergo standardised procedures but end up with less-than-predictable results in terms of weight loss, impact on obesity-related T2D and long-term weight regain (King et al., 2019). As a result, there is still an unmet need for other approaches to the treatment of obesity and associated T2D. The gut hormones, led by GLP-1, have emerged over the past few years as a potential answer to this need. This review will discuss the rationale for combination gut hormone therapies, the latest clinical evidence underpinning these therapies, and will conclude with some important unanswered questions regarding the prospects for these therapies.

GLP-1: the gut hormone path-finder

Glucagon-like peptide 1 (GLP-1) is the most extensively studied gut hormone with translational and clinical evidence for its efficacy (Holst, 2007). It is an alternatively processed product of the proglucagon peptide, secreted from neuroendocrine L-cells in the small intestine in response to nutrient ingestion. GLP-1 has pleiotropic roles, famously as an incretin hormone, stimulating glucose-dependent insulin secretion from β cells (Drucker and Nauck, 2006). Additional physiological effects include suppression of glucagon secretion from α cells (likely via stimulation of δ cell paracrine somatostatin secretion) (Campbell and Drucker, 2013), inhibition of gastric emptying and small bowel motility (Nauck et al., 2011), suppression of appetite and food intake leading to subsequent weight loss (Naslund et al., 2004, Bagger et al., 2015), and cardioprotective and anti-inflammatory effects (Marx and Libby, 2018). GLP-1 analogues that incorporate resistance to dipeptidyl dipeptidase-IV (DPP-IV) breakdown and other modifications that enable convenient daily or even weekly dosing are

now in routine clinical use, examples being exenatide, lixisenatide, liraglutide, dulaglutide, albiglutide, and semaglutide. The efficacy of these drugs in ameliorating T2D as judged by HbA1c has been well proven. Moreover, the glucose-dependence of the insulin release occasioned by GLP-1 minimises the risks of hypoglycaemia. GLP-1 analogues are now firmly established in international treatment pathways (Buse et al., 2020). Oral GLP-1 analogues (Pratley et al., 2019) are now approved and are likely to expand the numbers of people with T2D taking this class of medications.

Given that GLP-1 analogues were associated with appreciable weight loss effects when given for T2D (Potts et al., 2015), it was natural to examine their effects when given for obesity as the primary indication, for example, the SCALE Phase 3 trials demonstrated that liraglutide at doses of 3 mg daily led to a placebo corrected 4% mean weight loss (Pi-Sunyer et al., 2015). Greater magnitudes of weight loss were obtained in a Phase 2 trial of liraglutide's successor, semaglutide, which achieved 13.8% weight loss at the 0.4 mg/day dose vs 11.2% with liraglutide 3 mg/day and 2.3% for placebo. However, this enhanced efficacy was associated with more frequent adverse events, mainly nausea, diarrhoea, constipation and vomiting (O'Neil et al., 2018).

As alluded to, GLP-1 has protective effects on the cardiovascular system, including anti-inflammation, ischaemic cardioprotection, natriuresis and diuresis, inhibition of platelet aggregation and suppression of postprandial lipid excursions (Drucker, 2016). These benefits have been borne out in a series of cardiovascular outcome trials in the context of T2D with established cardiovascular disease or at high risk for such disease, such as ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN-6 (semaglutide), EXSCEL (exenatide LAR), HARMONY Outcomes (albiglutide), REWIND (dulaglutide) and PIONEER-6 (oral semaglutide). As a class, these drugs reduce major adverse cardiovascular events by 12%, death from cardiovascular causes by 12%, fatal or non-fatal stroke by 16%, fatal or non-fatal myocardial infarction by 9% and all-cause mortality by 12%, hospital admission for heart failure by 9%. Moreover, the trials provide evidence for benefits for kidney disease where a composite kidney outcome (development of new-onset macroalbuminuria, a decline in estimated glomerular filtration

rate/increase in serum creatinine, progression to end-stage kidney disease, or death attributable to kidney causes) is reduced by 17%, mainly driven by a reduction in urinary albumin excretion (Kristensen et al., 2019). GLP-1 analogues are now recommended for people with T2D who are at high risk of cardiovascular disease (Buse et al., 2020).

A *post hoc* analysis of the SCALE trials in people with obesity (who were not specifically selected for high risk of cardiovascular disease) has suggested that there is a reduction in cardiovascular events (hazard ratio 0.42) with high-dose liraglutide but with wide confidence intervals (0.17-1.08) (Davies et al., 2018). In comparison, other treatments for obesity have either demonstrated adverse cardiovascular outcomes (e.g. sibutramine) or appear to be neutral/safe in this respect (e.g. lorcaserin). Dedicated cardiovascular outcomes trials for this treatment indication are required to definitively demonstrate cardiovascular safety (and, hopefully, benefit) in this population and are forthcoming (e.g. SELECT: ClinicalTrials.gov NCT03574597).

To summarise, GLP-1 analogues are mature clinical treatments for T2D and obesity. However, at the highest doses, patients commonly experience gastrointestinal side effects, typically nausea, vomiting, alterations in bowel habit and abdominal pain, which limits the dose that can be given. Moreover, GLP-1 does not increase (or may even reduce) energy expenditure in humans (Flint et al., 2000). As a result, the magnitude of weight loss observed with GLP-1 analogues, although valuable, is limited with 1 in 3 failing to achieve a minimal 5% weight loss even with high-dose liraglutide (Pi-Sunyer et al., 2015). As a result, investigators have considered the use of GLP-1 in combination with other gut hormones that may bring complementary benefits, and this has led to a search for suitable partners or partner activities as outlined in the following sections.

GIP: twinning with GLP-1

Glucose-dependent insulinotropic polypeptide (GIP) is the partner incretin to GLP-1. GIP is secreted by neuroendocrine K cells in the duodenum and jejunum in response to nutrient ingestion. GIP is

thought to have a ‘stabilizer’ effect on glucose levels: during hyperglycaemia, GIP is insulinotropic but does not alter glucagon release, whereas during hypoglycaemia it increases glucagon release (hence increasing glucose levels) and does not affect insulin secretion (Christensen et al., 2011). At first blush, this might make GIP an ideal partner for GLP-1, but other properties of GIP make it less than desirable for the treatment of obesity and diabetes. GIP promotes lipid deposition in subcutaneous adipocytes in the context of obesity and T2D, possibly leading to further exacerbation of these conditions (Thondam et al., 2017). Unlike GLP-1, GIP does not reduce appetite and the combination of GLP-1 with GIP does not lead to any more significant appetite reduction than GLP-1 alone (Bergmann et al., 2019). GIP’s insulinotropic actions and amelioration of glycaemia are impaired in the context of T2D. As a result, some investigators have even explored the idea of GIP antagonism as a concept for therapy (Gasbjerg et al., 2018), but the potential of this approach is not yet clear.

A ray of hope for GIP comes from the observation that in the context of T2D, insulin therapy and normalization of glucose levels restores the favourable incretin effects of GIP (Hojberg et al., 2009), opening the possibility that a GLP-1/GIP combination (dubbed a ‘twincretin’) might be effective, the GLP-1 leading to normalisation of glycaemia and enabling GIP to exert its beneficial effects. Although short-term co-infusion studies of GLP-1/GIP do not show any decided advantage of the combination over GLP-1 alone (Daousi et al., 2009, Bergmann et al., 2019, Gasbjerg et al., 2019), twincretin drugs are nevertheless being pursued by the pharmaceutical industry (Finan et al., 2013). The early results from Lilly’s twincretin tirzepatide have created some excitement in the area. Tirzepatide is a unimolecular agonist of GLP-1 and GIP with a deliberate bias towards GIP over GLP-1 activity (Coskun et al., 2018). When tested in Phase 2 in people with T2D and obesity, tirzepatide appears to have significantly superior effects on glycaemia and weight loss in comparison to the benchmark GLP-1 analogue dulaglutide, although this seems to occur at the expense of more gastrointestinal side effects (Frias et al., 2018). Novo Nordisk’s twincretin, NNC0090-2746, has more balanced GLP-1 and GIP activity and early clinical trials of this analogue have shown improvements in HbA1c and weight over

placebo when given over 12 weeks' treatment, although the performance of NNC0090-2746 did not appear markedly better than the benchmark GLP-1 analogue liraglutide (Frias et al., 2017).

To summarise, it is currently difficult to reconcile the superior efficacy reported from the tirzepatide trials with the failure to show any substantive enhancement of physiological effects with the co-infusion of GLP-1 and GIP. Nevertheless, if the currently published data from tirzepatide is borne out in larger clinical trials, this is quite a promising prospect for therapy.

Proglucagon peptides working side by side: GLP-1/glucagon agonism

Glucagon is the metabolic hormone generated by the canonical processing of proglucagon in the alpha cells that classically antagonises the actions of insulin, by stimulating the catabolism of glycogen and gluconeogenesis to release glucose, and of fat deposits to release fatty acids for β-oxidation and hepatic ketogenesis. Less appreciated effects of glucagon include insulinotropy, appetite suppression and increases in energy expenditure. Moreover, glucagon increases hepatic fat oxidation and represents an approach to ameliorating fatty liver disease (Finan et al., 2019). These observations suggest that glucagon may be a complementary partner for GLP-1 by improving weight loss through synergistic suppression of appetite and increased energy expenditure, and proof-of-concept physiological studies by our group have confirmed this (Cegla et al., 2014, Tan et al., 2013). However, glucagon has the undesired effect of provoking hyperglycaemia (Scott and Bloom, 2018). Our studies showed that GLP-1 contributes to this partnership by ameliorating the hyperglycaemia provoked by glucagon (Tan et al., 2013, Cegla et al., 2014).

A natural unimolecular GLP-1/glucagon dual agonist exists in the shape of oxyntomodulin, a 37 amino acid peptide that is co-secreted with GLP-1 from the L-cells of the small intestine as an additional product of the differential processing of proglucagon in the gut (Holst et al., 2018). Oxyntomodulin reduces food intake and increases energy expenditure, leading to significant weight loss in a 28-day

clinical study in human volunteers over 28 days (Wynne et al., 2006), and has been shown to improve insulin secretion in short-term clinical studies in people with diabetes (Shankar et al., 2018).

As a result of this promising data, GLP-1/glucagon dual agonists are under active development (Figure 1). Cotadutide is an example of a 'balanced' unimolecular dual agonist with equivalent GLP-1 and glucagon activities which has been shown in Phase 2 trials in people with obesity and T2D to significantly improve glycaemic tolerance to a meal stimulus and to reduce body weight by 2-3 kg in comparison to placebo (Ambery et al., 2018, Parker et al., 2020). Another dual agonist, SAR425899, has been shown in Phase 1 trials to reduce HbA1c by up to 0.75% in the context of T2D and body weight by up to 5 kg or so (Tillner et al., 2019).

In summary, GLP-1/glucagon dual agonists are promising candidates for the treatment of T2D and obesity. However, we await definitive data to establish whether these dual agonists are superior to GLP-1 analogues. Glucagon's hyperglycaemic activity might reverse some of the signal improvements in glycaemia seen with GLP-1 alone, and this may make these dual agonists less suitable for clinical situations characterised by more marked dysglycaemia.

Peptide YY: walking the straight and narrow

Peptide YY (PYY) is another gut hormone that is co-secreted from the L cells with GLP-1 and oxyntomodulin. It exists in two major forms: the full length PYY(1-36) peptide that binds to the neuropeptide Y1, Y2, Y4 and Y5 receptors; and the PYY(3-36) peptide which is derived from PYY(1-36) via processing by DPP-IV, this binds to the neuropeptide Y2 and Y5 receptors. PYY(3-36)'s chief action of interest for obesity therapy is appetite suppression, which is mediated by Y2 receptors in the arcuate nucleus, and infusion of PYY(3-36) in human volunteers induces a 33% reduction in food intake over 24 hours (Batterham et al., 2002). Early clinical studies utilising a nasal preparation of PYY(3-36) showed, however, that the efficacy in terms of weight loss was limited by dose-dependent nausea and vomiting (Gantz et al., 2007), because of an rapid 'burst' release of PYY to supraphysiological levels.

When PYY levels are increased slowly to physiological levels, suppression of food intake is obtained with better tolerability and less nausea (Batterham et al., 2002). This narrow therapeutic range means that slower release profiles are necessary to mitigate nausea and vomiting (Rangwala et al., 2019) and to enable weekly delivery of treatment, e.g. Novo Nordisk's PYY1875 (Novo Nordisk, 2019).

In infusion studies, the combination of PYY(3-36) and GLP-1 confers better appetite suppression than each individual peptide (Neary et al., 2005). The neurophysiological basis of this phenomenon has been investigated using Blood Oxygen Level Dependent (BOLD) functional MRI imaging studies. These show that brain areas implicated in appetite and interest in food are activated when subjects are shown pictures of food. PYY(3-36) and GLP-1 given individually reduce the activation of these areas. The co-infusion of PYY(3-36) and GLP-1 led to a synergistic effect with near-suppression of these areas, correlating with the suppression in appetite as assessed by food intake studies (De Silva et al., 2011). Co-administration of PYY(3-36) and oxyntomodulin had also an enhanced appetite suppression compared to each peptide alone (Field et al., 2010). However, in contrast to GLP-1, PYY does not seem to have a marked effect on glucose-stimulated insulin secretion when given to human volunteers. Moreover, PYY does not add to the insulinotropic effect of GLP-1 (Tan et al., 2014). Therefore, there is ample physiological data to substantiate the added value of PYY(3-36) in terms of appetite suppression and improving weight loss, but PYY(3-36) may not have any immediately added value on glycaemia in the context of diabetes, although with enhanced weight loss, PYY(3-36) may contribute in the longer term.

Considering these factors, the likelihood is that PYY analogues will be employed in combination with GLP-1 to enhance the weight loss with GLP-1 analogues alone (Figure 1). However, there is currently a relative paucity of published clinical studies with this class of agents to substantiate their efficacy and tolerability when given long-term.

Triagonism: is three better than two?

By blending three complementary gut hormone actions, we may be able to obtain advantages over dual agonism. Surgery, and in particular RYGB, exerts many of its beneficial effects by activating the exaggerated release of GLP-1, oxyntomodulin and peptide YY after eating, leading to improvements in glucose metabolism, suppression of appetite and reductions in body weight (le Roux et al., 2007, Abdeen and le Roux, 2016). Building on this observation, we used a subcutaneous infusion pump to deliver a combination of GLP-1/oxyntomodulin/PYY(3-36) (GOP) at doses to replicate the elevated post-prandial levels found after RYGB (Tan et al., 2017). When this GOP combination was given for up to 12 hours per day for 28 days in obese people with T2D or prediabetes we showed that GOP infusion achieves superior glucose tolerance and reduced glucose variability compared with RYGB and has a favourable effect on body weight, although energy expenditure was not enhanced, at least with the doses used (Behary et al., 2019). Our proof-of-concept study suggests that triple agonism of the GLP-1, glucagon and Y2 receptors using the GOP combination may possess advantages even over RYGB, hitherto considered the standard-of-care for treatment of obesity and diabetes, and further studies are planned to explore the doses and combinations to obtain optimal efficacies and to substantiate the concept.

Other groups have explored the concept of GLP-1/GIP/glucagon triagonism to obtain extra benefits from adding the benefits of glucagon action (promotion of energy expenditure and amelioration of fatty liver disease) to the 'twincretin' effects of GLP-1 and GIP (Figure 1). These properties were combined in the design of the unimolecular triagonist MAR423 with promising results in animal models which have been taken forward to an ongoing Phase 1 trial (Brandt et al., 2018). HM15211 is another triagonist compound which has shown favourable pre-clinical data in animal models of steatohepatitis (Finan et al., 2015, Tschop et al., 2016, Jall et al., 2017) and which is currently in Phase 1 trials.

Some questions for the future

What are the optimal combinations and doses of gut hormone activities? The combination approach brings complications in terms of selecting the optimal balance of receptor agonistic activities. Animal models are helpful in the pre-clinical selection of this balance for development (Day et al., 2009) but it must be borne in mind that these models do not completely replicate the human physiological situation: for example, GLP-1 increases energy expenditure in rodents but not in humans. Therefore, pre-clinical data on drug candidates should be interpreted with caution. Further long-term physiological clinical studies are required to define the balance of receptor agonism that leads to optimal outcomes.

Will combination therapies inherit the favourable effects on clinical outcomes demonstrated by GLP-1 analogues? Although the scientific and clinical evidence for GLP-1's benefits on clinically valuable endpoints such as cardiovascular and renal disease in the context of T2D is reasonably developed, such evidence is lacking in the context of obesity treatment and is currently lacking for any of the combination analogues. Moreover, the effects of the combination partner activities may be undesirable: for example, GIP may carry pro-inflammatory and pro-atherosclerotic effects (Heimburger et al., 2020). Assuming the new combination gut hormone therapies do deliver enhanced weight loss and glycaemic control in forthcoming Phase III trials, it will be crucial to see if the beneficial effects of GLP-1 over-ride any potential undesirable effects from partner hormone activities.

Is a unimolecular agonist the correct approach, or do individuals require customised balancing of activities? Many of the developmentally advanced dual analogues (e.g. tirzepatide and cotadutide) have been unimolecular analogues which have modified a basic gut hormone sequence to add in or enhance receptor activity, arriving at a specified balance of activities for each drug. Although this approach makes development simpler, this approach assumes that one balance will fit all. Clinical experience with GLP-1 analogues shows that there is a considerable intraindividual variation in response to dosing, e.g. in terms of weight loss and tolerability (Pi-Sunyer et al., 2015); logically, there

will be a variation of response to the relative balance of hormone activities with dual or triple agonists. To obtain a truly optimal response on multidimensional outcomes (weight loss/glycaemia/cardiovascular protection/long-term tolerability etc.) individuals may require customised balancing of activities; however, the technical, practical and regulatory hurdles to such an approach are more difficult to surmount than the well-trodden path of unimolecular analogue development.

What is the cost-effectiveness and sustainability of gut hormone analogue therapy? Bariatric surgery, for all its shortcomings, is accepted as cost-effective, as are lifestyle interventions (Gulliford et al., 2017, Avenell et al., 2018). The institution responsible for cost-effectiveness assessment in the UK, the National Institute for Health and Care Excellence (NICE) has assessed the cost-effectiveness of GLP-1 analogues in the treatment of T2D and these are now recommended (National Institute for Health and Care Excellence, 2015). On the other hand, liraglutide 3 mg for the obesity indication has not yet been recommended by NICE, as of writing, primarily because cost-effectiveness estimates range up to £105,000 per Quality-Adjusted Life Year (QALY), much higher than the acceptable limit of £20,000 to £30,000 per QALY (National Institute for Health and Care Excellence, 2020). One key driver of this uncertainty over the cost-effectiveness is how long analogue therapy will be given beyond a treatment length of 2 years; another is the paucity of direct evidence for cardiovascular benefit when liraglutide is employed in this context. These uncertainties, as well as a sustainable pricing model, will need to be resolved to enable those who need it to access treatment.

What is the place of gut hormone analogue treatment in the journey of people with obesity? To date, the trials of GLP-1 analogues have to a large extent concentrated on demonstrating their efficacy and safety on a minimal baseline of diet and exercise advice delivered in a clinical trial context. Some trials have demonstrated that analogues have an added value on top of a lifestyle intervention, for example, the SCALE-Maintenance trial showed that liraglutide 3 mg could induce a mean weight loss of 6% on top of a weight loss of 6% induced by a run-in low calorie diet (Wadden et al., 2013). However,

it is currently unclear whether an analogue is best employed as an induction therapy followed by maintenance with lifestyle change, versus induction with lifestyle change followed by analogue therapy. There is also uncertainty as to how long analogue treatment should last: discontinuation of liraglutide after 56 weeks' treatment leads to an upwards drift in weight (Wadden et al., 2013), and there is no clear guidance as to whether analogue therapy should continue for longer. Gut hormone treatment cannot be regarded as a 'silver bullet' for obesity and T2D, rather, they will have a place within a personalised and integrated program for weight and metabolic management that incorporates lifestyle, dietary change as well as psychological support and an element of coaching. Pragmatic trials to understand the best sequence to employ these management tools within such a framework are sorely needed.

Conclusion

Combination gut hormone drugs utilising GLP-1 as the mainstay are likely to appear as marketed therapies for T2D and obesity within the forthcoming decade, and there is a real prospect of these medications delivering improved weight loss and glycaemic control over presently available analogues (Figure 1). Many questions remain, however, as to what the right combination is, how they work, and how best to employ these new medications. To answer these questions, the pharmaceutical and scientific communities will need to gather evidence from a wide range of studies ranging from long-term physiological studies to randomised controlled trials and, crucially, pragmatic trials of treatment models to bridge the gap between Phase 3 study and real-life practice. Only then will we be able to realise the full potential of gut hormone therapy.

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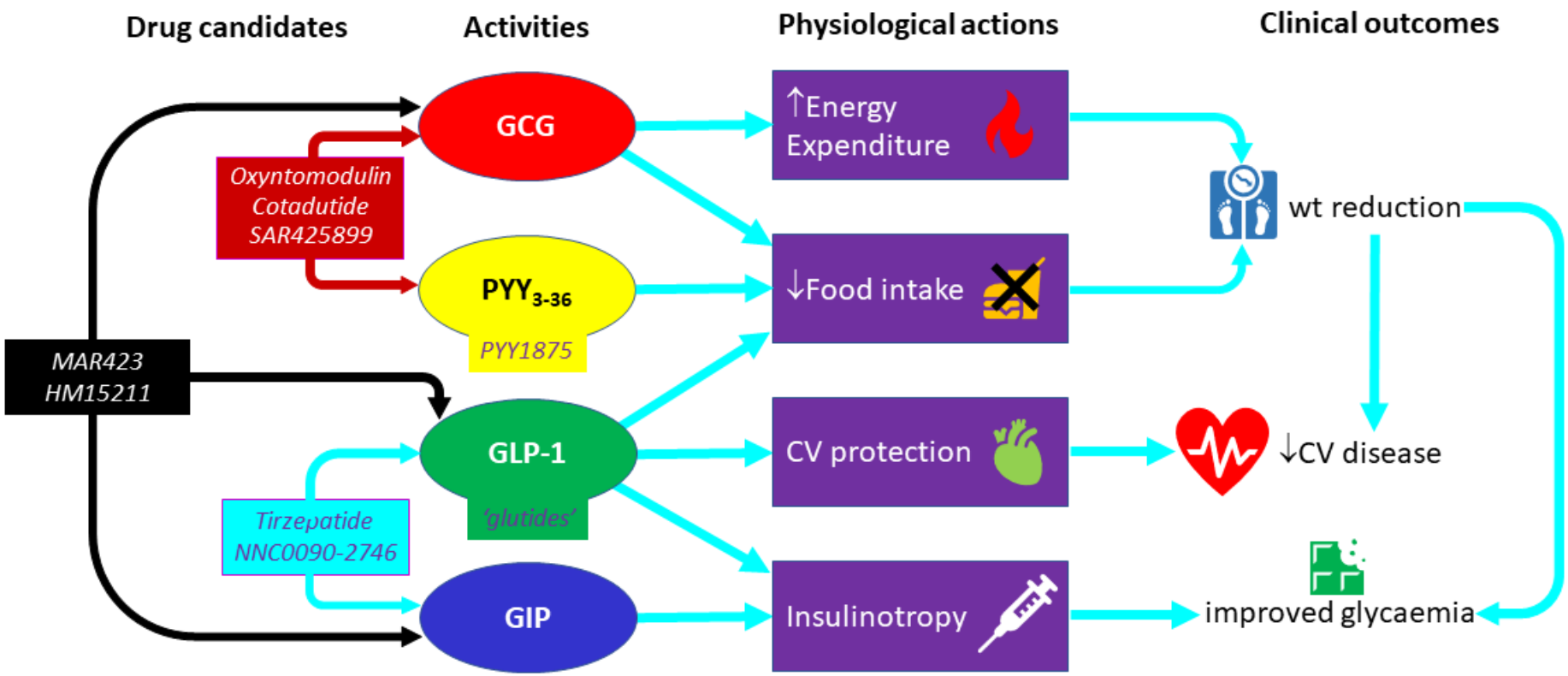

Figure 1: Schematic figure showing the relationship between combination gut hormone drug candidates, the hormonal activities stimulated, their physiological actions and the envisaged clinical outcomes. GCG, glucagon; PYY, peptide YY; GLP-1, glucagon-like peptide-1, GIP, glucose-dependent insulinotropic peptide; CV, cardiovascular.