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Will medications that mimic gut hormones or target their receptors eventually replace bariatric surgery?

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ABSTRACT

Bariatric surgery is currently the most effective therapeutic modality through which sustained beneficial effects on weight loss and metabolic improvement are achieved. During recent years, indications for bariatric surgery have been expanded to include cases of poorly controlled type 2 (T2DM) diabetes mellitus in lesser extremes of body weight. A spectrum of the beneficial effects of surgery is attributed to robust changes of postprandial gut peptide responses that are observed post operatively. Consolidated knowledge regarding gut peptide physiology as well as emerging new evidence shedding light on the mode of action of previously overlooked gut hormones provide appealing potential obesity and T2DM therapeutic perspectives. The accumulation of evidence from the effect of exogenous administration of native gut peptides alone or in combinations to humans as well as the development of mimetic agents exerting agonistic effects on combinations of gut hormone receptors pave the way for future integrated gut peptide-based treatments, which may mimic the effects of bariatric surgery.

1. Introduction

Obesity, defined as excess body adiposity, has reached pandemic proportions over the last decades, among all age groups [1]. The mainstay of weight loss strategies has traditionally been lifestyle modification. Dietary strategies lead to sustained weight loss in a minority of cases only, mainly due to adaptative changes in the mechanisms regulating appetite that eventually lead to increased food intake [2].

The algorithm for the treatment of obesity and, more recently, type 2 diabetes mellitus (T2DM), has undergone a gradual change of perspective since the introduction of bariatric surgery almost 70 years ago [3]. Advances in available surgical modalities and new insights into the humoral mechanisms of post-surgical weight loss and metabolic reconstitution have directed the evolution of obesity and diabetes management towards a new concept. Following bariatric surgical procedures, substantial and durable weight loss responses are typically observed [4–6], accompanied by sustained favorable effects on insulin sensitivity, glucose tolerance and glycemic control in T2DM [6–11]. Subsequently, indications for bariatric surgery have been expanded to include cases of inadequately controlled T2DM, even in patients with lower body mass indexes [12]. Naturally, the use of the term "metabolic surgery" has gradually gained ground against that of "bariatric". Furthermore, the positive effects of bariatric surgery come at the expense of a reasonable, albeit existent, peri-operative and long-term risk [13–16].

Ongoing research has provided compelling evidence regarding the role of gut peptides as key mediators of the beneficial effects of bariatric surgery. Furthermore, certain aspects of the physiology and role in metabolic regulation of various gut hormones have been elucidated in bariatric surgical models, paving the way for their potential use as targets for obesity and T2DM therapy. Hence, it could be claimed that future gut-peptide based medical approaches may outweigh surgical treatment or at least integrate surgery in multi-modality obesity and

Abbreviation: AG, Acylated ghrelin; AgRP, Agouti-related peptide; BAT, Brown adipose tissue; BMI, Body mass index; CVD, Cardiovascular disease; DIO, Diet induced obesity; DPP4, Dipeptidyl-Peptidase-4; DVC, Dorsal vagal complex; EMA, European Medicines Agency; FDA, Food and Drug Administration; FPG, Fasting plasma glucose; GHSR1a, Growth hormone secretagogue receptor type 1a; GI, Gastrointestinal; GIP, Glucose-dependent insulinotropic peptide; GLP-1, Glucagon-like peptide 1; GLP-2, Glucagon-like peptide 2; GLP1R, Glucagon-like peptide 1 receptor; GOAT, Ghrelin-O-acyltransferase; GRPP, Glicentin- related pancreatic polypeptide; IGT, Impaired glucose tolerance; IP-1, Intervening peptide 1; NPY, Neuropeptide Y; OXM, Oxyntomodulin; PC, Proprotein convertase; POMC, Proopiomelanocortin; PYY, Peptide tyrosine-tyrosine; RYGB, Roux-en-Y gastric bypass; SCT, Secretin; SG, Sleeve gastrectomy; T2DM, Type 2 diabetes mellitus; UAG, Unacylated ghrelin.

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T2DM therapeutic schemes. Herein, current evidence regarding the gut peptides' physiology and their role in weight loss after bariatric surgery is reviewed, along with the evolving aspects in the field of gut peptide-based obesity and T2DM therapies.

1.1. Metabolic effects of bariatric surgery

An obvious effect of bariatric surgery is the establishment of a state of reduced caloric intake as a consequence of reduced hunger and increased satiety mediated by changes in subcortical brain areas involved in appetite control. These changes are a consequence of targeted anatomical modifications of the gastrointestinal tract. Surgery therefore does not work mostly through restriction or malabsorption but rather through reduction in hunger, increases in satiety or a combination of both. Human studies have unveiled an accessory weight-loss mediating role for increases in both resting energy expenditure [17,18] and diet induced thermogenesis [19–21], as well as alterations in gut hormones [22], bile acid metabolism [23] and gut microbiota [24–26].

Additionally, post bariatric surgery, a number of beneficial changes are noted regarding glucose metabolism. Peri- and post-operative caloric restriction and weight loss per se lead to substantial improvements in whole-body insulin sensitivity and glucose tolerance [27]. However, additional contributors to these phenomena may be sought in weight loss-independent functional changes in the gastrointestinal tract. Those include, among others, improvements in first-phase insulin secretion, increased gut glucose utilization, altered bile acid physiology and changes in postprandial gut peptide responses [27].

In addition, bariatric surgery ameliorates liver steatosis and inflammation in the vast majority of cases of non-alcoholic fatty liver disease and steatohepatitis. Improvements in liver biochemistry, fat content and histology are observed within months following surgery [28–30]. In turn, this interrupts the vicious circle of hepatic steatosis and insulin resistance [31] and may account for a portion of the beneficial effects on glycemic control that follow bariatric operations.

2. Overview of gut hormones involved in the regulation of hunger and satiety

2.1. Predominantly foregut-secreted peptides

2.1.1. Ghrelin

Ghrelin is a 28-aminoacid orexigenic gut hormone, secreted by P/D (1)-type (X/A-like) enteroendocrine cells which are most abundant in the gastric body but are also found in other sections of the gastrointestinal (GI) tract and the pancreas [32]. Ghrelin results from the cleavage of a 117-aminoacid pro-hormone by proprotein convertase (PC) 1/3 and is subsequently acylated in the third serine residue by the enzyme ghrelin-*O*-acyl transferase (GOAT) in the endoplasmic reticulum [33]. GOAT is also present in human plasma, in levels that positively correlate with body mass index (BMI) [34]. Acylated ghrelin (AG) is biologically active and binds the growth hormone secretagogue receptor type 1a (GHSR1a). Animal studies have shown an abundance of ghrelin receptors in brain areas involved in the regulation of hunger and satiety, such as the hypothalamic arcuate, paraventricular, ventromedial and dorsomedial nuclei, the ventral tegmental area [35] and the area postrema in the brainstem [36]. The orexigenic neuropeptide Y (NPY) and Agouti-related peptide (AgRP) secreting neurons in the arcuate nucleus are crucial for the mediation of the appetite-stimulating effects of ghrelin [37], as shown by the attenuation of these effects in NPY-KO or AgRP-KO [38] and NPY/AgRP neuron-ablated mice [39]. The binding of ghrelin on GHSR1a causes activation of NPY/AgRP neurons and a subsequent GABA-mediated inactivation of adjacent anorexigenic proopiomelanocortin (POMC) neurons [40]. In humans, neuroimaging using functional MRI has shown that intravenous ghrelin infusion modulates neural activity in brain regions implicated in hedonic food intake, such as the amygdala and the orbitofrontal cortex [41]. Peripheral administration of ghrelin has been shown to increase ad libitum energy intake in rodents [42] and in man [43]. Ghrelin infusion has also been shown to accelerate gastric emptying in healthy humans [44].

Additionally, in mice and rats ghrelin reduces energy expenditure by a GSHR-mediated suppression of thermogenesis in brown adipose tissue (BAT) [45–47].

Certain glucoregulatory effects may be exerted by unacylated ghrelin (UAG), specifically increases in insulin sensitivity and secretion [48–50]. In this context, its actions seem to oppose those of AG, attributing a possible relevance to the AG/UAG ratio [48,51]. Plasma ghrelin levels are normally increased during prolonged fasting and suppressed immediately after food intake. In states of increased adiposity, lower fasting plasma total and acylated ghrelin levels are observed, coupled with a blunted postprandial ghrelin suppression [52]. On the other hand, the higher plasma GOAT concentrations observed in morbid obesity may imply a counteracting role for this molecule against adaptively lower plasma ghrelin levels in obese states [34].

2.1.2. Secretin

Secretin (SCT) is a 29-aminoacid peptide chiefly secreted by the S-cells in the proximal intestine [53] in response to increased acidity and protein and fat digestion products in the duodenum after meal intake [54]. Its biological actions are mediated through its G protein-coupled receptor SCTR [55]. Acknowledged for a long time for its stimulatory effects on aqueous exocrine pancreatic secretion and the inhibition of gastric emptying and acidic secretion [54,56–58], previously unacknowledged actions have been recently attributed to secretin. In preclinical studies, the expression of secretin and its receptor was ascertained in various regions of mouse and rat brain, including areas crucial for the regulation of energy intake such as the arcuate [59], paraventricular and supraoptic hypothalamic nuclei [59,60] and the area postrema and nucleus of the solitary tract in the brainstem [61]. Peripheral SCT may also indirectly affect central appetite-regulating nuclei through afferent vagal pathways [62]. Moreover, Cheng et al. demonstrated that intraperitoneal or intraventricular SCT administration in mice inhibits food intake, an effect prominent in wild-type and SCT (−/−) but not SCTR (−/−) animals, which was chiefly mediated by the activation of POMC neurons within the ARC [59]. SCT has been also shown to induce lipolysis in mouse adipocytes in vitro and in vivo [63]. A recent breakthrough in the understanding of the role of secretin on energy balance came from the works by Li, Schnabl et al., who confirmed the presence of SCTR in abundance in mouse mature brown adipocytes [64]. Therein, SCT was shown to potently and acutely induce UCP-1 – mediated uncoupled respiration (a component of non-shivering thermogenesis) [65]. Furthermore, the satiating effect of SCT was attenuated in UCP-1 KO mice, suggesting a central role of SCT-activated BAT in mediating these effects and hence the presence of an additional check-point in the gut-brain axis [64]. The thermogenesis-inducing effect of SCT was also demonstrated in human BAT [64].

2.1.3. Glucose-dependent insulinotropic polypeptide (GIP)

Glucose-dependent insulinotropic polypeptide (GIP) is a 42-aminoacid peptide secreted mostly from the K-enteroendocrine cells in the duodenum and proximal jejunum in response to nutrient ingestion [66]. GIP interacts with its specific receptor (GIPR) on pancreatic beta cells to induce glucose-dependent insulin secretion (incretin effect). Unlike Glucagon-like peptide 1 (GLP-1) however, it has no effect on gastric emptying [67], or induction of satiety [68],while it also stimulates glucagon secretion in normoglycemic conditions [69]. GIP is generally considered to have negligible direct effects on the regulation of appetite and energy expenditure, with the possible exception of indirect glucagon-mediated modulating actions on the latter [70]. GIP receptors are present on adipocytes, where it has been shown to enhance glucose uptake, lipoprotein lipase activity and fatty acid esterification in rodents [71], lean [72] and obese [73] humans. The anabolic effects of GIP in adipose tissue are, at least partly, attributable to enhancement of insulin

secretion and potentiation of its actions at the adipocyte cellular level [71]. Studies involving GIP signaling modulation in rodent models of obesity have yielded equivocal results. GIPR-knockout mice are protected against diet induced- and leptin deficiency induced obesity, while selective knockout of GIPR in pancreatic beta cells has been similarly shown to protect from diet-induced obesity suggesting an obesogenic role of GIP [71]. In contrast, Kim et al. demonstrated that mice overexpressing GIP are also protected from obesity in an over-nutrition setting [74].

2.2. Predominantly hindgut-secreted peptides

2.2.1. Proglucagon gene products

The proglucagon (GCG) gene, located in chromosome 2, is chiefly expressed in alpha cells of pancreatic islets and L-enteroendocrine cells of the distal gastrointestinal tract. Its primary translational product is proglucagon, which undergoes cell-specific post translational modification resulting in different final secretory products. Thus, dominance of PC2 action in alpha cells results in glucagon as the main product, while cleavage by PC 1/3 yields, among others, Glucagon-Like Peptide 1 (GLP-1), Oxyntomodulin, Glucagon-Like Peptide 2 (GLP-2) and Glicentin, along with other peptides of undetermined significance [75]. All PC 1/3-derived proglucagon related products are secreted by the L-cells following meal ingestion, together with PYY.

2.2.2. GLP-1

GLP-1 results from cleavage of proglucagon and is secreted as GLP-1 (7–37) and GLP-1 (7–36)-NH2 which constitute its biologically active forms [76]. GLP-1 is the main (along with GIP) effector of the incretin effect [77]. Apart from the glucose-dependent increase in insulin secretion, GLP-1 actions on the pancreatic beta cell include induction of the proinsulin gene and anti-apoptotic effects leading to beta-cell mass preservation [77]. Additional metabolic attributes of GLP-1 include inhibition of glucagon secretion from pancreatic alpha cells [77], delaying of gastric emptying and modification of hunger and satiety [78]. The mechanisms behind GLP-1-mediated satiety induction have been extensively studied in animal models which have highlighted the significance of peripheral GLP-1 production by L-enteroendocrine cells as well as locally secreted GLP-1 in appetite-regulating brain regions. In rats, the GLP-1 receptor (GLP1R) is broadly expressed in CNS areas implicated in the regulation of energy intake, such as the arcuate, dorsomedial, and paraventricular hypothalamic nuclei, the area postrema and the nucleus of the solitary tract [79] and the ventral tegmental area of the mesolimbic reward system [80]. In rodent hypothalamus, GLP-1 signaling activates POMC and deactivates NPY/AgRP neurons [81,82]. GLP1R are also present on gastrointestinal vagal axon termini. As with other gut derived satiety stimuli (i.e. gastric distension) GLP-1 induces afferent vagal input in the medullary dorsal vagal complex (DVC) (which includes the nucleus of the solitary tract and the area postrema) [83]. Projections from the DVC reach important nuclei implicated in energy intake such as the ventral tegmental area of the mesolimbic reward system, the paraventricular and arcuate nuclei [83]. The net effect of the peripheral and central actions of gut-derived postprandial GLP-1 secretion is the suppression of appetite and inhibition of food intake [84].

2.3. Oxyntomodulin

The oxyntomodulin (OXM) peptide chain is structurally homologous to glucagon, with a C-terminal extension of the 8-aminoacid Intervening Peptide-1 (IP1) [85]. OXM exhibits agonistic effects on both GLP-1 (GLP1R) and glucagon receptors (GCGR) [86]. Likewise, the complex biological effects of OXM resemble those of both peptides and include a weak incretin-like action, delayed gastric emptying, increased hepatic glucose output and lipolysis [85], appetite suppression and increased energy expenditure [85,87]. Interaction with GLP1R and GCGR cannot account for the whole spectrum of OXM effects and hence, actions on additional receptors or even the presence of an OXM-specific receptor have been proposed [86].

2.3.1. GLP-2

GLP-2 is a 33-aminoacid peptide secreted in equimolar amounts to GLP-1 from L-cells which specifically acts on its G-protein-coupled receptor (GLP2R) [88,89]. GLP1R antagonist exendin serves as a functional antagonist of GLP2R-mediated effects [90]. GLP2 exerts a trophic effect on intestinal lining by inducing proliferation and inhibiting apoptosis of enterocytes [91]. Rodent studies have shown GLP2R localization in the compact part of the dorsomedial nucleus, on POMC neurons in the arcuate nucleus [92] and the nucleus of the solitary tract [93], while mice that lack GLP2R on POMC neurons in the arcuate nucleus exhibit increased food intake, meal frequency, and more rapid gastric emptying [92]. In a study by Baldassano et al., peripheral administration of native GLP-2 or a GLP2R agonist resulted in decreased energy intake in lean and, to a lesser degree, in diet induced obese (DIO) mice. This effect was blocked by the co-administration of a GLP2R antagonist or exendin, while there were no additive anorectic effects after co-administration of GLP-1 [94]. Intraventricular administration of GLP-2 also suppresses food intake in rats, an effect blocked by exendin [90,95]. Corresponding data in humans are scarce, but in a study by Schmidt et al., no effect was found on satiety scores or gastric emptying by intravenous GLP-2 infusion [96].

2.3.2. Glicentin

Glicentin is an additional product of proglucagon cleavage by PC 1/3 in L enteroendocrine cells. The structure of glicentin incorporates the sequences of three distinct components of the proglucagon gene product, namely glicentin- related pancreatic polypeptide (GRPP), glucagon and IP-1, hence including the sequences of both oxyntomodulin and glucagon in its 69-aminoacid chain [97]. The biological role of glicentin is still a matter of active research, in part due to the lack of reliable methods for its quantitative estimation until recently. Evidence from in vitro and animal studies show that it promotes intestinal mucosal trophicity and functional integrity [98,99], and may also have insulinotropic and inhibitory effects to glucagon secretion [100,101]. Regarding human studies, lower fasting glicentin circulating levels have been found among adolescents with obesity, impaired glucose tolerance (IGT) or T2DM [102] and adults with severe or morbid obesity [103]. A causative role of glicentin in obesity and related conditions remains uncertain.

2.4. Peptide tyrosine-tyrosine (PYY)

PYY is postprandially secreted by the L enteroendocrine cells in the distal ileum and colon, in amounts related to the caloric content and macronutrient composition of the meal [104]. PYY1–36 is released as a 36-aminoacid protein which undergoes cleavage by dipeptidyl-peptidase 4 (DPP4) to form PYY3–36. Animal studies have highlighted the appetite-reducing effects of the selective binding of PYY3–36 to presynaptic G protein-coupled Y2 receptors (Y2R), hence inhibiting NPY/AgRP and activating POMC neurons in the arcuate nucleus [105,106]. In rats, the anorexigenic effects of PYY3–36 are attenuated after pre-treatment with a Y2R antagonist [107] while they are absent in Y2R-KO mice [106]. PYY3–36 action on Y2R present in vagal fibers may contribute to appetite suppression, inducing afferent satiety signals projecting on the nucleus of the solitary tract in rats [108]. A study in humans using functional MRI neuroimaging demonstrated that PYY3–36 administration to achieve postprandial plasma concentrations modulates hypothalamic and corticolimbic brain activity in correlation to feeding behavior [109]. Obesity in humans is associated with lower fasting and postprandial circulating PYY concentrations [110,111], while exogenous administration of PYY3–36 to lean and obese individuals results in potent appetite suppression [111]. The anorexigenic effects of pharmacologic PYY3–36 agonism have been also

shown to be dose-dependent [112]. Apart from the induction of satiety, PYY exhibits additional physiologic actions of interest to glucose regulation, such as delaying of gastric emptying, inhibition of insulin secretion and potentially promotion of the survival of beta-cells [104,113,114]. Studies on the effect of PYY3–36 on energy expenditure in humans have yielded ambiguous results, with existing reports in support of the implication of PYY3–36 in increased thermogenesis [115] and others in which no effect was observed [116,117]. For an overview of the effects of foregut and hingut produced peptides plese see Fig. 1 and Table 1.

2.5. Effects of bariatric surgery on gut peptides

The effect of the various bariatric surgical operations on the endocrine physiology of the gastrointestinal tract is a field attracting major investigatory and clinical interest, with observational and mechanistic studies exploring the differential effects of bariatric surgery on gut peptide mobilization. Improvements in the incretin effect which is impaired in the dysmetabolic cascade of events leading to dysglycemia and T2DM are observed promptly after Roux-en-Y gastric bypass (RYGB) as well as sleeve gastrectomy (SG) [118–120]. According to the "hindgut hypothesis", this may be a consequence of the volume-restricted gastric residue which allows for a rapid transit of unabsorbed nutrients to the GI segments distal to the stomach, which then subsequently elicit an enhanced secretion of GIP and GLP-1 from enteroendocrine cells [118,119,121–123]. Specific effects may relate to the type of surgery; the duodenum and proximal jejunum, where GIP-secreting K-enteroendocrine cells are in abundance, is typically bypassed in RYGB and this may be the reason behind the less pronounced changes or even reductions in GIP secretion and action after RYGB [122,124–126]. OXM levels are also enhanced post-RYGB in response to an oral glucose load [126,127] and correlate with corresponding increases of GLP-1 and PYY [127], suggesting the "hindgut hypothesis" as a common mechanism for all three peptides. In recent work from our study group, postprandial OXM levels rise potently during the months following SG in a degree comparable to that of RYGB. Furthermore, postprandial levels of OXM three months after surgery positively correlate with subjectively assessed satiety scores and predict weight loss at 6 and 12 months after surgery (unpublished data from our group).

Glicentin is the least researched molecule of the proglucagon family. Raffort et al. reported a gradual increase in fasting glicentin levels after both SG and RYGB, peaking at 12 months postoperatively (1.6- and 2-fold increase respectively), but these changes did not correlate with weight loss or glycemic improvement [128]. Additionally, higher fasting glicentin concentrations have been shown to predict postprandial hypoglycemia in post-RYGB patients [129]. Furthermore, in a manner similar to OXM, percent postprandial increases of glicentin 3 months post-operatively showed high correlation with satiety scores and prospective weight loss at 6 and 12 months after surgery (unpublished data from our group). Altogether, these features suggest a potentially important role of glicentin in weight loss and the glycemic improvements observed after bariatric surgery.

Data regarding post-operative effects on secretin physiology are scarce. Increased SCT expression in the jejunum of RYGB-operated rats has been reported [130]. However, existing evidence from human studies contradict this observation. Nergård et al. reported no change in the density of SCT-producing cells in proximal alimentary limb biopsies of super-obese, non-T2DM individuals 12 months post RYGB [131]. In a study among obese T2DM and normoglycemic individuals, Rhee et al. demonstrated decreased secretin mRNA expression in jejunal biopsies 10 months after RYGB compared to those obtained perioperatively [132].

Robust post-operative changes are also observed in peptides specifically regulating hunger and satiety. SG results in decreased fasting and postprandial plasma ghrelin levels [133,134], probably as a result of the surgical removal of a large proportion of the stomach and the subsequent decrease in ghrelin-secreting cell mass [133,134]. Satiety-inducing PYY levels are elevated after RYGB and SG, both in the fasting state and after meal intake [126,133–135]. Apart from its anorexigenic effects, increases in PYY following surgery exert beneficial effects on beta-cell secretory function, and hence may be important determinants of restoration of euglycemia and T2DM remission [136,137].

3. Gut hormone-derived agents approved and under development for the treatment of obesity and T2DM

3.1. GLP-1 receptor agonists

GLP1R agonists for weight loss exploit the anorexigenic effects of GLP1R agonism previously demonstrated in animal models after native GLP-1 intraperitoneal [138], intravenous [139], or intracerebroventricular [140] administration, as well as after intravenous infusion in man [141]. Potential mechanisms include multifaceted modifications of central neuronal appetite signaling [142], or altered afferent signaling from taste receptors and upper gastrointestinal mechanoreceptors [143]. Due to the documented beneficial effects of GLP1R agonists on glycemia, they are particularly useful in the medical management of obesity-related T2DM [144]. Among the adverse effects associated with the use of GLP1R agonists, the most common are gastrointestinal disturbances such as nausea, vomiting, diarrhea and dyspepsia which typically subside in the course of continued treatment. Furthermore, there have been concerns regarding the induction of pancreatic tissue inflammation, symptomatic pancreatitis or pancreatic neoplasms and small increases in heart rate [145]. Currently, the only Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved GLP1R agonist for the treatment of obesity is liraglutide. In the SCALE study program, liraglutide at a daily dose of 3.0 mg added to lifestyle modification showed an excess mean of 4.2 and 5.6 kg weight loss against placebo after 56 weeks among individuals with and without T2DM, respectively [146]. Furthermore, among those without T2DM, after 3 years of treatment, liraglutide was associated with a sustained greater weight loss and a lower rate of progression to T2DM [147]. Other drugs in this class such as dulaglutide and especially semaglutide have shown promising results regarding weight loss in T2DM Phase 3 trials [148–150]. Furthermore, semaglutide was tested in increasing daily doses (0.05–0.4 mg) in a phase 2 clinical trial conducted among individuals with obesity without T2DM. With regard to weight loss at 52 weeks, all tested semaglutide doses were significantly superior compared to placebo (loss of 6–13.8% of total body weight vs 2.3%, respectively) while doses exceeding 0.2 mg were superior to liraglutide 3 mg daily (11.2–13.8% of total body weight vs 7.8%) [151]. Semaglutide has been also formulated in an orally absorbed tablet form, which makes it the first gut-peptide based therapy available via the oral route. An early (phase 2) clinical trial showed superiority for the oral form against placebo in glycemic improvement and weight loss among patients with T2DM treated with lifestyle modification and/or metformin while the effect of higher doses (10–40 mg daily) was comparable to that of the weekly 1 mg SC dose [152]. The antihyperglycemic and weight loss efficacy and safety of oral semaglutide against placebo and various active comparators were tested in the phase 3 PIONEER trial program. After 26 weeks of treatment, oral semaglutide was found to be superior to placebo in reducing HbA1c in all tested doses and body weight at 14 mg daily [153], while the efficacy and safety of the 14 mg daily dose among individuals with stage 3 chronic kidney disease was ascertained in the PIONEER 5 study [154]. Additionally, compared to subcutaneous daily liraglutide, oral semaglutide was found to be equally effective in reducing HbA1c while achieving greater reductions in body weight [155]. It was superior regarding both endopoints compared to oral sitagliptin [156]. Furthermore, in the respective cardiovascular safety trials, daily liraglutide and weekly semaglutide were found to be safe and effective in reducing major cardiovascular adverse events in the LEADER and SUSTAIN-6 trials among T2DM patients with a substantial cardiovascular risk [157,158], while liraglutide showed an additional overall mortality benefit [158].

In those trials, benefits were noted among individuals with established cardiovascular disease (corresponding to 81.3% of LEADER and 83% of SUSTAIN-6 participants). Significant benefits regarding the manifestation of the triple composite outcome (cardiovascular death, nonfatal myocardial infraction or stroke) were recently announced in the results of the cardiovascular safety trial for weekly dulaglutide versus placebo (REWIND), in which cardiovascular disease was established in only 31% of participants with T2DM. In REWIND, results regarding the primary outcome were similar within the subgroups of participants with and without established cardiovascular disease (p for interaction 0.97), a finding which highlights the potential application of dulaglutide for primary cardiovascular prevention in high risk individuals with T2DM [159]. In the cardiovascular outcome trial for oral semaglutide (PIONEER 6), the agent did not reduce the primary composite cardiovascular outcome, while achieving non-inferiority against placebo [160].

3.2. Ghrelin O-acyltransferase (GOAT) inhibitors

The ghrelin-activating enzyme (GOAT) constitutes an attractive candidate target for the medical therapy of obesity and metabolic dysregulation. Apart from the blockade of the orexigenic effects of AG, inhibition of GOAT may potentially affect glucose regulation by modifying the AG/UAG ratio [48,50]. So far, evidence on the effect of GOAT blockade is derived solely from animal studies. Although knockout of the GOAT gene does not affect weight in normally fed mice [161], it protects from high-sucrose diet-induced obesity [162]. Octanoylated pentapeptides, structurally homologous to the N-terminal chain of ghrelin, lead to effective, albeit weak GOAT inactivation [163]. A specific GOAT inhibitor introduced by Barnett et al. was shown to improve glucose tolerance and prevent weight gain in wild type but not ghrelin-deficient mice after intraperitoneal injection [164]. Intraperitoneal administration of the same inhibitor in rats resulted in a decrease in meal frequency without affecting meal size [165].

3.3. PYY analogs

The dose-dependent anorexigenic effects of PYY3–36 in lean and obese individuals [111,112] render it an attractive target for the medical treatment of obesity and T2DM, although any attempts may be hindered by the plasma short half-life of PYY3–36. Subcutaneous injections of escalating doses of PYY3–36 did not influence ad libitum energy intake among males with obesity, despite the induction of subjectively assessed satiety [166].

3.4. Oxyntomodulin and GLP-1/glucagon dual agonists

Both GLP-1 and glucagon agonism promote weight loss through distinct but overlapping mechanisms that include the induction of satiety and increases in energy expenditure. Furthermore, the GLP-1 receptor-mediated insulinotropic actions could counteract the hyperglycemic attributes of glucagon [167]. The exploitation of these properties could find clinical application in the treatment of obesity. In fact, intravenous co-administration of both molecules was shown to acutely increase energy expenditure with a concomitant blunting of glucagon-induced hyperglycemia [168] and furthermore reduce ad libitum energy intake at subanorectic doses of each individual compound [169] in overweight and obese volunteers.

Oxyntomodulin exerts agonistic effects on both GLP-1 and GCG receptors (although with a lower affinity than the native peptides), thereby exhibiting a combination of insulinotropic, anorexigenic, and energy expenditure-increasing actions [86]. Human studies have highlighted the efficacy of the administration of the native OXM peptide in reducing food intake and body weight and improving glycemia. Intravenous OXM infusion in healthy volunteers was shown to decrease plasma ghrelin levels, while also inducing satiety and leading to diminished acute and 12 h ad libitum energy intake by 19.3% and 11.3%, respectively [170]. In a study conducted among participants who were overweight or obese, a TID subcutaneous OXM self-administered injection for 4 weeks resulted in significantly greater weight reduction versus placebo (2.3 vs. 0.5 kg, $p < 0.05$), with documented significant decreases in energy intake during an ad libitum test meal at the beginning and end of the 4 week period [171]. Likewise, TID subcutaneous OXM administration for 4 days was shown to both reduce energy intake and augment total energy expenditure in people with obesity [87]. Regarding the acute effects of OXM on glucose homeostasis, a logical concern could be raised that any beneficial GLP1R agonism would be blunted by a glucagon-like physiologic action. In a recent study however, intravenous OXM administration was shown to increase insulin secretion rates and mitigate glucose excursions during a graded glucose infusion in subjects with obesity plus/minus T2DM [172]. The observed effects were similar (though to a lower degree) to those of SC liraglutide. As with other gut peptides, pharmacologic administration of OXM would be hampered by its considerably short plasma half-life (~12 min) [86]. In order to overcome this, several analogs with longer plasma half-life or even increased affinity to GLP-1 and GCG receptors have been developed and are under study [173–175].

A similar rationale led to the development of dual GLP-1/glucagon receptor agonists which have shown promising results regarding weight loss and amelioration of glucose intolerance in animal studies [176,177]. A number of relevant compounds are currently under evaluation [178], while early-phase placebo-controlled human trials have yielded promising results in the short term; phase 1 testing of the SAR425899 dual agonist showed efficacy in reducing fasting plasma glucose (FPG), HbA1c, and body weight in healthy normal-to-overweight and T2DM-overweight-to-obese individuals [179]. Similarly, in a phase 2a trial conducted among people with T2DM who were overweight or obese, another GLP-1/glucagon dual agonist (MEDI0382) resulted in a significantly greater weight loss (−3.84 vs. −1.70 kg), reductions in FPG (−2.8 vs. −1.1 mmol/L), HbA1c (−0.9% vs −0.6%) and liver fat content (−39.12% vs. −19.51% relative fat content) and a comparable adverse event profile to placebo, after 41 days of daily SC administration [180].

3.5. Other dual and triple agonists

Apart from research on synthetic GLP1/GCG receptor dual agonists which can be viewed as an expansion of attempts towards OXM agonism, a broader tempting concept is the concomitant exploitation of the pharmacologic actions of different gut peptide analogs, in order to achieve synergistic or complementary beneficial effects. Several double and triple gut peptide agonist combinations are currently under development or undergoing testing for weight loss and/or T2DM [178,181]. GIP and GLP-1 both exhibit incretinic potential but they also possess features exclusively relevant to each individual peptide. Examples include the hunger-suppressing effects of GLP-1 or the adipose-tissue anabolic actions of GIP, as well as the opposite effects of the two molecules regarding glucagon secretion from alpha cells [66,182]. Finan et al. were the first to report the efficacy of a synthetic fatty-acylated dual agonist possessing in vitro balanced GIPR and GLP-1R agonism (NNC0090-2746) in promoting weight loss and improving insulin secretory rates across different species, including DIO and ob/ob obese mice, monkeys and humans [183]. In a 12-week phase 2a trial, NNC0090–2746 was found to be superior to placebo in body weight and HbA1c reduction, with an adverse event frequency similar to that of liraglutide, while also exhibiting benefits in plasma lipid profile not typically seen in GLP1R agonist monotherapy [184]. In a recent phase 2b trial, the antihyperglycemic efficacy of the weekly dual GIP/GLP-1R agonist tirzepatide (LY3298176) in different doses was examined among patients with inadequately controlled lifestyle- or metformin- treated T2DM against that of dulaglutide and placebo. After 26 weeks, tirzepatide was found to be superior to dulaglutide 1.5 mg at all doses exceeding 1 mg weekly, with dose-dependent reductions in HbA1c ranging from −1.6% for 5 mg/w to −2.4% for 15 mg/w

(all $p < 0.05$) [185]. Likewise, meaningful reductions in body weight (a secondary endpoint of the study) were observed, which were also dose-dependent (weight loss at 26 weeks: 2.7 kg for dulaglutide and 4.8, 8.7, and 11.2 kg for tirzepatide 5, 10 and 15 mg, respectively) [185]. These benefits came at the expense of a significantly higher rate of gastrointestinal adverse effects compared with dulaglutide, with diarrhea reported more frequently among participants in the tirzepatide 5, 10 and 15 mg groups, while nausea, vomiting or treatment discontinuation due to an adverse event were more prevalent in the 15 mg group compared to that of dulaglutide [185].

The above mentioned demonstrated gains from glucagon or GIP co-agonism with GLP-1 gave rise to the concept of developing agents exerting triple agonistic effects on GIP, GLP-1 and glucagon receptors [186–189]. Finan et al. reported the development of a GIP/GLP-1/glucagon triagonist with increased affinity for each corresponding receptor than each native peptide. The compound exhibited weight loss and glycemic benefits attributable to combined agonism of all 3 receptors [189]. Another GIP/GLP-1/glucagon triagonist is in phase 1 clinical testing (NCT03374241, NCT03744182).

Trials involving PYY3-36 co-administration with other gut peptides have also shown positive results. In a study of 12 normal weight males, preprandial combined oral GLP-1 and PYY3–36 intake mixed with a vector for oral delivery [sodium N-[8-(2-hydroxybenzoyl) amino]caprylate)] acutely suppressed ad libitum energy intake by 21.5% while that of PYY3–36 alone had no significant effects [190]. In another study of 12 males who were overweight or obese, concomitant intravenous infusion of PYY3-36 and oxyntomodulin reduced ad libitum energy intake during a test meal by 42.7% compared to placebo, and significantly more than each compound alone [191]. Significant additive effects have been documented regarding appetite suppression and decreases in voluntary energy intake after combined infusion of PYY3–36 and GLP-1 in rodents and humans [116,192]. A PYY analog in

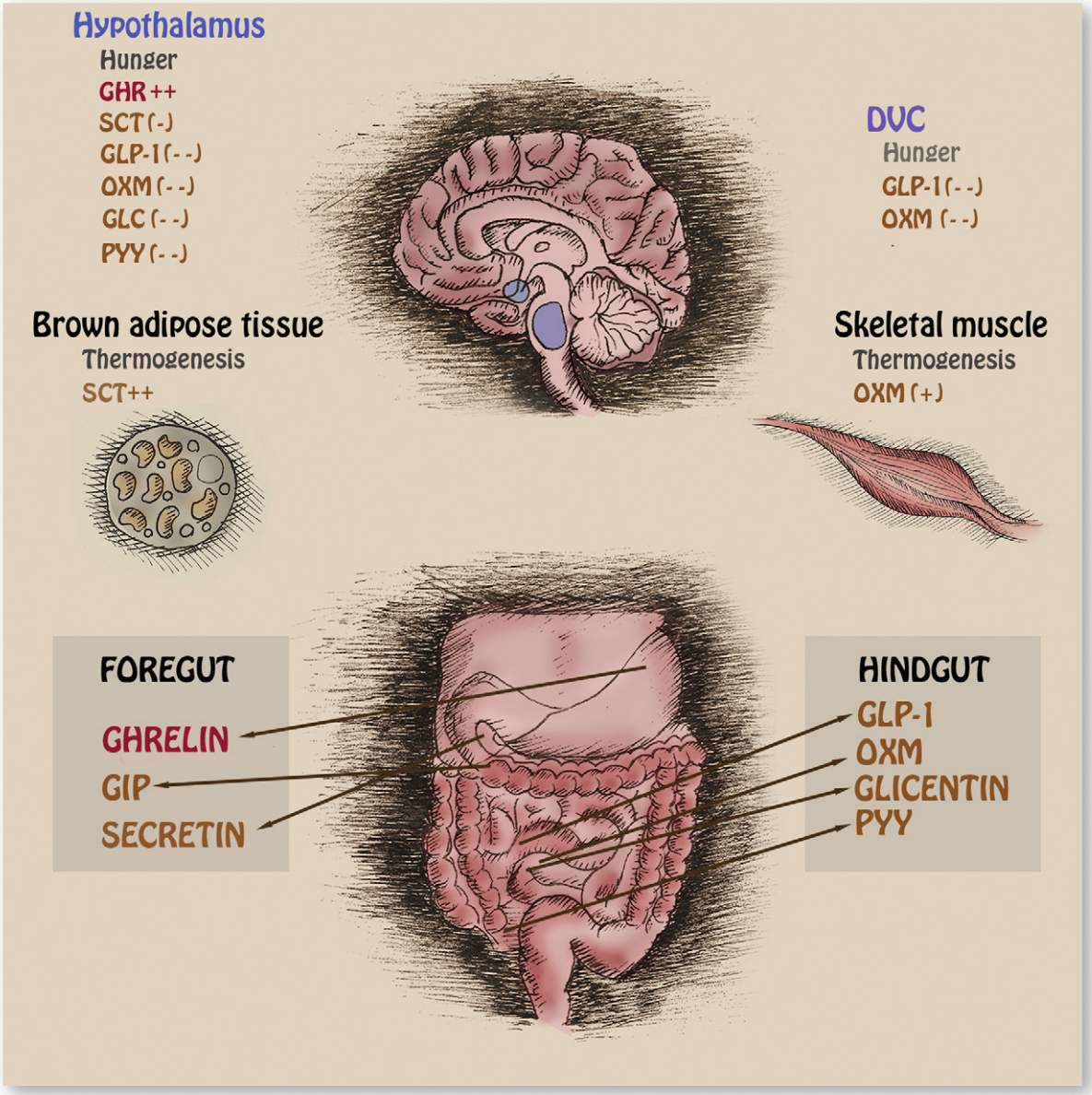

Fig. 1. Key gastrointestinal hormonal mediators of hunger and energy expenditure. Hormonal peptide signals from the foregut and hindgut act on the hypothalamus and brainstem to induce or suppress hunger. Secretin is part of a gut-brown adipose tissue-brain axis and promotes thermogenesis in BAT and satiety in the hypothalamus. Oxyntomodulin also increases energy expenditure through a possible effect on skeletal muscle thermogenesis. Dual, triple, or multiple combinations of synthetic peptide agonists could pave the way for a "medical bypass". GHR: Ghrelin, GIP: Glucose-dependent insulinotropic peptide, SCT: Secretin, GLP-1: Glucagon-like-peptide-1, OXM: Oxyntomodulin, GLC: Glicentin, PYY: Peptide tyrosine-tyrosine.

Table 1
Main modes of action implicated in metabolic effects of different gut peptides. Arrows in bold and normal font indicate evidence from human and animal studies, respectively. Transverse arrows indicate a neutral effect while a dash (−) notes a lack of sufficient evidence.

Peptide	Appetite	Energy expenditure	Insulin Secretion	Intestinal lining	Gastric emptying	Adipose tissue
Foregut-secreted peptides						
Ghrelin	↑↑ ↑↑	↓	↓↑[a]	(−)	↑	↑
GIP	↔	↔	↑↑ ↑↑	↔	↔	↑↑
Secretin	↓	↑↑	↑	(−)	↓↓	↓
Hindgut-secreted peptides						
GLP-1	↓↓	↔	↑↑ ↑↑	↔	↓↓	↓↑
OXM	↓↓	↑↑	↑↑	↔	↓	↑
GLP-2	↓	↔	↔	↑↑ ↑↑	↔	↔
Glicentin	↓	(−)	↑	↑	↔	(−)
PYY	↓↓ ↓↓	↑↔	↓	(−)	↓↓	↓

[a] Differential effects of acylated and unacylated ghrelin.

combination with GLP1R agonist semaglutide (NCT02568306) is currently undergoing phase 1 trial testing.

GUB06-046, a long half-life dual SCTR/GLP1R agonist was shown to reduce energy intake and lead to glycemic improvements in db/db obese diabetic mice (albeit to a lesser degree than liraglutide) along with inducing increases in beta-cell mass without affecting exocrine pancreatic tissue mass [130].

3.6. Future directions: integrating complementary approaches towards the "Medical Bypass"

Anatomical changes and functional adaptations following bariatric surgery lead to altered gut peptide kinetics. Changes in individual peptide levels and postprandial mobilization have been reviewed above. It is clear that virtually the whole constellation of gut peptides play a role in this phenomenon, including those selectively secreted from different segments of the gastrointestinal tract, namely the proximal (ghrelin, GIP, secretin) and distal gut (PYY, proglucagon products).

In contrast, until recently, most gut peptide-mimetic pharmaceutical attempts intended for weight loss and metabolic amelioration have been utilizing single-agonist approaches with a fair rate of success, as evidenced by the results of clinical trials and accumulating clinical experience with GLP1R agonists. An increasing body of preclinical and emerging clinical evidence, however, has unveiled the additive benefits from the combination of double or multiple gut peptide agonists, in order to draw the maximum potential of their complementary physiological actions. In a profound way, this would resemble the dynamic changes regarding gut peptide responses following bariatric surgery. Tan et al. recently investigated the effect of a triple GLP-1/OXM/PYY ("GOP") subcutaneous infusion in individuals with obesity but without diabetes on appetite and energy expenditure. They reported a 32% reduction in ad libitum energy intake during two meals over a span of 10.5 h and a neutral effect on energy expenditure [193]. The novelty of this study should be traced not only in the choice of combined agents, which resembled closer than ever before the gut peptide battery secreted postprandially by the L-enteroendocrine cell, but more importantly in the selected doses of administration. Specifically, infusion rates (4, 4 and 0.4 pmol/kg/min for GLP-1, OXM and PYY, respectively) were tailored to achieve plasma levels comparable to those observed postprandially in a group of age- and BMI-matched individuals that had previously undergone RYGB surgery. Of note, in the same study, similar reductions in energy intake with the use of each agent separately were observed at infusion rates multiple to those of the triple combination [193]. Furthermore, in a recent study by Behary et al., a continuous daily 12-hour subcutaneous GOP infusion at the same rate (4/4/0.4 pmol/kg/min) for 4 weeks in obese patients with T2DM or prediabetes was well tolerated and resulted in greater weight loss than saline placebo (4.4 kg vs. 2.5 kg). Even though the effect on body weight and fat mass loss was more moderate compared to a group of post-RYGB participants and to another assigned a very low calorie diet (<800 kcal/day) for the same amount of time, improvements in glycemic variability and glucose tolerance during a mixed meal tolerance test were more pronounced among individuals in the GOP infusion group [194].

Altogether, these facts foretell a switch of the future perspective in gut peptide-based obesity and T2DM therapies towards a more integrated approach, exemplified by the increasing understanding of post-bariatric surgery hormonal adaptations on one hand, and the relative contribution of each individual of these changes to the achievement and maintenance of weight loss and glycemic improvement on the other. Undoubtedly, there is a long way ahead in the field of gut peptide-based therapies in order to achieve clinical results comparable in magnitude and sustainability to those of metabolic surgery. Current and upcoming research, however, is providing steps towards that goal. The potential future availability of analogs to hitherto overlooked players of the gut peptide inventory (i.e. glicentin mimetics, secretin receptor agonists, GOAT inhibitors) may provide additional components for the eventual integration of the "medical bypass" as a competitive alternative to surgery, which could be used not merely for patients with an unacceptable operative risk, but to a broader spectrum of people suffering from obesity and T2DM.

Even if the medical bypass does not prove to be as efficient as the surgical one, in truth it doesn't have to be, provided it is scalable and can help a large number of patients. It should also not present a hindrance against other treatments for obesity and T2DM, even surgical

Table 2
Agents targeting gut-peptide receptors indicated or under evaluation for the treatment of obesity and/or T2DM.

Agent	Target						Clinical stage					Indicated/Tested	
	GLP1R	GCGR	GIPR	Y5 (PYY)	SCTR	GOAT	Marketed	Phase 3	Phase 2	Phase 1	Preclinical	T2DM	Obesity
Liraglutide	+						+					+	+
Dulaglutide	+						+					+	
Exenatide	+						+					+	
Semaglutide	+						+	(+)				+	(+)
Lixesenatide	+						+					+	
Tirzepatide	+		+					+				+	
NNC0090–2746	+		+						+			+	
Unnamed (ref. 174)	+	+	+								+	+	+
HM15211	+	+	+							+			+
SAR425899	+	+								+		+	+
MEDI0382	+	+							+			+	+
GUB06–046	+				+						+	+	+
NNC0165–1562				+						+			+
GO-CoA-Tat						+					+	+	+

ones. Since a variety of different procedures with fairly distinct mechanisms of action are offered (i.e. purely gastric vs. combination of gastric and intestinal rearrangements), targeted gut peptide-based medical therapies could be offered alongside specific surgical approaches, in order to compensate for the pathophysiological shortcomings of each procedure and thus improve therapeutic outcomes. This could enable the option of minimally invasive surgery in patients who are not eligible for complex procedures or serve as a complimentary option in the most difficult of cases. This last notion was further demonstrated by the results of a recent study by Miras et al., in which patients with T2DM with persistence or recurrence of T2DM after SG or RYGB were randomized to receive 1.8 mg of daily liraglutide or placebo, alongside lifestyle management for 26 weeks. Individuals in the liraglutide arm exhibited clinically significant benefits in glycemic indices (a reduction in HbA1c of 1.22% compared to placebo) irrespective of the type of previous bariatric surgery [195].

4. Conclusion

The increasing understanding of the physiology of gut peptides combined with their implication into the mechanisms leading to weight loss and metabolic improvement after bariatric surgery have enriched the treatment of obesity and T2DM with novel therapeutic perspectives. GLP1R agonists have been in clinical use already for more than a decade while more gut peptide mimetics are in various clinical trial phases and others have yielded promising results in pre-clinical studies. Future development of combined agonists or the utilization of combinations of agonists targeting multiple gut peptide receptors may serve as an effective alternative or accessory to bariatric surgery. (See Table 2.)

Author contributions

AK and CSM prepared the outline of the manuscript. All authors contributed in the writing of the manuscript, reviewed and approved its final version.

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