REVIEW

Unraveling oxyntomodulin, GLP1’s enigmatic brother

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Abstract

Oxyntomodulin (OXM) is a peptide secreted from the L cells of the gut following nutrient ingestion. OXM is a dual agonist of the glucagon-like peptide-1 receptor (GLP1R) and the glucagon receptor (GCGR) combining the effects of GLP1 and glucagon to act as a potentially more effective treatment for obesity than GLP1R agonists. Injections of OXM in humans cause a significant reduction in weight and appetite, as well as an increase in energy expenditure. Activation of GCGR is classically associated with an elevation in glucose levels, which would be deleterious in patients with T2DM, but the antidiabetic properties of GLP1R agonism would be expected to counteract this effect. Indeed, OXM administration improved glucose tolerance in diet-induced obese mice. Thus, dual agonists of the GCGR and GLP1R represent a new therapeutic approach for diabetes and obesity with the potential for enhanced weight loss and improvement in glycemic control beyond those of GLP1R agonists.

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Introduction

As the prevalence of type 2 diabetes increases, there is a medical need for additional antihyperglycemic agents that offer improved efficacy in glycemic control and tolerability. Obesity is an important risk factor for a number of debilitating chronic conditions such as T2DM, dyslipidemia, and hypertension (Bray 2004). However, several T2DM therapies have been associated with weight gain, most profoundly for the sulfonylureas, meglitinides, and thiazolidinediones (TZDs) as well as for insulin. Recent work on understanding the physiological function of proglucagon-derived peptides has renewed interest in glucagon-based therapeutics. One of these peptides is glucagon-like peptide-1 (GLP1), which is secreted from the L cells of the gastrointestinal tract and lowers blood glucose levels primarily by promoting insulin secretion and by inhibiting glucagon secretion (Holst 2000). GLP1 has been found to decrease food intake and inhibit gastric emptying (Holst 2000, D’Alessio 2008). GLP1 is rapidly inactivated by dipeptidyl peptidase-4 (DPP4) and its renal clearance is relatively fast (Field et al. 2009). Accordingly, new drugs based on GLP1 receptor (GLP1R) agonism and DPP4 inhibition have been approved for the treatment of type 2 diabetes, but the magnitude of weight loss at tolerated doses is modest (Amori et al. 2007). Nevertheless, protease-resistant GLP1R agonists (Drucker et al. 2010, Htike et al. 2012, Nauck 2012) represent a new class of antihyperglycemic agents that reduce body weight (D’Alessio 2008, Vilsboll et al. 2012) and are currently being tested for the treatment of obesity (Astrup et al. 2012).

The preproglucagon family: historical overview and tissue-specific posttranslational processing

Oxyntomodulin (OXM) is a 37-amino acid peptide secreted in proportion to nutrient ingestion (Ghatei et al. 1983, Le Quellec et al. 1992, Holst 1997, Drucker 2005) comprising the entire 29-amino acid sequence of glucagon, with an 8-amino acid carboxy-terminal extension that results from the processing of the preproglucagon precursor (Fig. 1; Campos et al. 1994, Larsen et al. 1997). The processing of proglucagon is tissue specific, producing from a single protein different hormones depending on the tissue considered. In pancreatic α cells, prohormone convertase 2 (PC2) generates predominantly glucagon (Rouille et al. 1994, Kieffer & Habener 1999, Furuta et al. 2001), whereas in intestinal L cells present in the jejunum, ileum, and colon, PC 1/3 predominantly produces glicentin, OXM, GLP1, and GLP2 (Ghatei et al. 1983, Le Quellec et al. 1992, Holst 1997, Drucker 2005, Brubaker 2012, Habib et al. 2012). Similar processing is also thought to occur in the same neurons in the nucleus of the solitary tract (NTS) in the hindbrain (Holst 2007, Fig. 1).
OXM binds to and is a full equipotent agonist of the human GLP1R and glucagon receptor (GCGR)-mediated cAMP accumulation, although with reduced affinity compared with the cognate agonists GLP1 and glucagon (Bataille et al. 1982, Baldissera et al. 1988, Gros et al. 1993, Schepp et al. 1996, Baggio et al. 2004, Jorgensen et al. 2007, Poci et al. 2009, Kosinski et al. 2012). Despite being a full agonist at the human GLP1R, OXM was found to be a full agonist in recruiting β-arrestin 2 to the GCGR, but partial agonists in recruiting β-arrestin 2 β-arrestin 1 and β-arrestin 2) and G-protein-coupled receptor (GPCR) kinase 2 to the GLP1R. Consistent with the properties of a partial agonist, OXM was a functional antagonist of GLP1-induced agonist response in β-arrestin 2 recruitment. It has been suggested that OXM is a GLP1R-biased agonist relative to GLP1 having less preference toward cAMP signaling relative to phosphorylation of ERK1/2, but similar preference for cAMP relative to Ca2+ (Jorgensen et al. 2007). These findings imply that the GLP1R–mediated in vivo effects of OXM could differ from that of GLP1 (Koole et al. 2010). Currently, no data are available on whether OXM interact with other family B GPCRs such as GLP2 and glucose-dependent insulinotropic peptide (GIP) receptors. Peripheral administration of OXM results in increased c-Fos in the arcuate nucleus (ARC), but not in the brainstem region (Dakin et al. 2004), and using manganese-enhanced magnetic resonance to follow the pattern of neuronal activation, OXM and GLP1 result in activation of different hypothalamic pathways (Chaudhri et al. 2006, Parkinson et al. 2009). While these differences may be simply due to a different brain penetration, it is plausible that the engagement of additional receptor(s) and/or the above reported difference on GLP1R signaling pathways may explain the differences.

OXM and body weight

OXM causes weight loss in obese patients (Wynne et al. 2005) and rodents (Dakin et al. 2001, Baggio et al. 2004) via...
suppression of food intake and increases in energy expenditure (Baggio et al. 2004, Wynne et al. 2006). OXM is a dual agonist at the GLP1R and GCGR in vitro (Baldissera et al. 1988, Gros et al. 1993, Pocai et al. 2009). The anorectic effects of central administrations of GLP1 and OXM are abolished by co-administration of the GLP1R antagonist, exendin(9–39), and are not observed in Glp1r−/− mice, suggesting that the central effect of OXM is mediated by the GLP1R (Turton et al. 1996, Dakin et al. 2001, Baggio et al. 2004, Sowden et al. 2007, Wynne et al. 2010). While data obtained with the truncated lizard peptide exendin(9–39) needs to be carefully evaluated as it was shown to function either as a GLP1 and GLP2 receptor antagonist and to displace GIP binding in vitro (Wheeler et al. 1995, Brubaker et al. 1997, Tang-Christensen et al. 2000), the lack of OXM efficacy seen in Glp1r−/− mice demonstrated that the initial anorectic effect of OXM is mediated solely by activation of the GLP1R. (Baggio et al. 2004, Sowden et al. 2007).

These data led several investigators to hypothesize that the differential effect of OXM vs GLP1 could be mediated by activation of the GCGR, or an as of yet unidentified OXM-specific receptor. Recently, several publications (Du et al. 2012, Kosinski et al. 2012) expanded the initial findings on the mechanism of action of OXM and demonstrated that OXM has glycogenolytic properties in perfused mice liver showing that OXM can functionally activate the GCGR. (Kosinski et al. 2012). Du et al. (2012) using a GLP1R agonist peptide with a mutation of Gln (Q) → Glu (E) (OXMQ3E) in position 3 that dials out activity on GCGR. (Santoprete et al. 2011; Fig. 2), demonstrated that OXM, but not OXMQ3E, stimulated liver ketogenesis in wild-type mice. A similar effect was observed in Glp1r−/− but not in Gcgr−/− mice demonstrating that this effect of OXM is mediated by GCGR activation (Du et al. 2012). When equimolar doses of OXM (GLP1R/GCGR dual agonist) and OXMQ3E (selective GLP1 agonist) were infused in obese mice, OXM exerted superior weight loss and lipid lowering with comparable glucose lowering to OXMQ3E (Kosinski et al. 2012). Moreover, chronic infusion of OXM in Glp1r−/− mice retained some of the body weight effect observed in lean wild-type mice, and pharmacological blockade of the GCGR during OXM infusion demonstrated that the additional body weight lowering observed with OXM vs OXMQ3E is mediated by activation of the GCGR. This study showed the involvement of the GCGR together with GLP1R activation to the body weight lowering effect of OXM, but it did not completely dismiss the potential contribution of an OXM-specific receptor as minor weight loss was observed in the group treated with a small molecule GCGR antagonist alone (Kosinski et al. 2012). The superior body weight loss efficacy of OXM vs GLP1R agonism is consistent with previous research on glucagon and energy homeostasis in humans and rodents. Repeated administration of glucagon was first shown to inhibit food intake in man over 50 years ago (Schulman et al. 1957), and aside from its well-known hyperglycemic action, glucagon increases thermogenesis, satiety, lipolysis, fatty acid oxidation, and ketogenesis (Salter 1960, Salter et al. 1960, Penick & Hinkle 1961, Langhans et al. 1982, Habegger et al. 2010, Jones et al. 2012). A critical physiological role of glucagon in the maintenance of whole-body energy homeostasis was supported by a recent study in T2D patients where a dose-dependent increase in body weight was observed following pharmacological blockade of the GCGR (Engel et al. 2011).

OXM and glucose metabolism

Studies have suggested that OXM may play a role in glucose homeostasis. Chronic treatment with OXM results in superior weight-lowering and comparable antihyperglycemic effect to a GLP1R-selective agonist (Kosinski et al. 2012). This is likely achieved through body weight reduction due to the causal link between obesity and type 2 diabetes (Karra & Batteram 2010) as well as direct enhancement of glucose-dependent insulin secretion (Maida et al. 2008, Parlevliet et al. 2008, Du et al. 2012). Activation of GCGR is associated with an elevation in glucose levels but the simultaneous agonism at the GLP1R would be expected to counteract this effect. Acute treatment with OXM improves glucose tolerance during a glucose challenge in mice (Maida et al. 2008, Parlevliet et al. 2008). Moreover, OXM administration improved glucose intolerance by enhancing glucose disposal during a hyperinsulinemic clamp study performed in diet-induced insulin-resistant mice (Parlevliet et al. 2008). It has been proposed that following a single injection, OXM acts solely via GLP1R to modulate glucose homeostasis (Maida et al. 2008). However, OXM was reported to increase hepatic glucose production during a euglycemic–hyperinsulinemic clamp performed in diet-induced obese mice, suggesting activation of the hepatic GCGR in vivo (Parlevliet et al. 2008). Recently, it was demonstrated that while acute treatment with OXM improves glucose metabolism during a glucose tolerance test and during a hyperglycemic clamp in mice, a matched pair peptide without GCGR activity (OXMQ3E) (Fig. 2) exerted better glucose-lowering properties compared with OXM administration (Du et al. 2012). The same authors

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GLP1 HAEFTFTSDVS SYLEGQAAKE FIAWLWKGR
Glucagon HSQGFYSDYS KYLSRRQQ AFVQWLMT
Glicentin RSQDTEKSSRSFASASADPLSDPQMQEDKR
HSQGFYSDYS KYLSRRQQ AFVQWLMTKRRNNNIA
OXM H3EFTFTSDYS KYLSRRQQ AFVQWLMT KRRNNNIA
OXMQ3E H3EFTFTSDYS KYLSRRQQ AFVQWLMT KRRNNNIA

Figure 2 Sequence comparisons of GLP1(7–36) amide, glucagon(1–29), glicentin, OXM, and OXMQ3E.

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showed decreased glucose tolerance in OXM-infused compared with vehicle-infused Glp1r−/− mice. The lack of effect observed following a single i.p. injection of OXM during a glucose tolerance test in Glp1r−/− mice (Maida et al. 2008) may be explained by the fact that Glp1r−/− mice are glucose intolerant and resistant to diet-induced obesity; hence, the acute glucoregulatory effect of a single injection of OXM could be confounded by compensatory mechanisms associated with chronic deletion of the GLP1R (Flamez et al. 1999). To further strengthen these data, hyperglycemic clamps performed in Gcgr−/− mice showed a similar effect of OXM and OXMQ3E infusion on glucose metabolism in the absence of a functional GCGR. This study demonstrated that simultaneous activation of the GLP1R counteracts the hyperglycemic effect of glucagon in vivo. The glucose-lowering effect of OXM is mostly mediated by GLP1R activation and activation of the GCGR appears to limit the acute antihyperglycemic efficacy of OXM while contributing to the insulinotropic properties of OXM (Du et al. 2012). Glucagon has been reported to increase glucose levels following i.c.v. administration in rats (Marubashi et al. 1985, Amir 1986). However, Migliiu et al. (2012) recently demonstrated that intrahypothalamic glucagon suppresses hepatic glucose production and counteracts the direct hepatic stimulatory effect of circulating glucagon on liver glucose production in rodents during a pancreatic clamp. Therefore, activation of the GCGR in discrete CNS areas may contribute to the improvement of whole-body glucose metabolism in animals treated with OXM.

Other actions of OXM

Gastrointestinal effects

OXM decreases gastric acid and pancreatic exocrine secretion (Bataille et al. 1981a, Dubrasquet et al. 1982, Ghatei et al. 1983, Biedzinski et al. 1987, Schjoldager et al. 1989, Le Quellec et al. 1992, Anini et al. 2000) and increases intestinal glucose uptake in preclinical species (Collie et al. 1997). Acute administration of OXM does not decrease gastric emptying in mice (Maida et al. 2008) while i.v. infusion of OXM inhibits gastric emptying in humans (Schjoldager et al. 1989). GLP1 is thought to reduce postprandial glucose excursion primarily via deceleration of gastric emptying in rodents and humans (Wettergren et al. 1993, Willms et al. 1996), although this effect seems to desensitize after multiple administrations (Meier et al. 2005, Nauck et al. 2011) and glucagon has also been reported to decrease gastric emptying (Habegger et al. 2010). Further studies are required to confirm or reconcile these divergent findings on gastric emptying in mice and humans potentially involved in the effect of OXM on the regulation of glucose and energy metabolism (Fig. 3).

Pancreatic effects

OXM has been reported to decrease pancreatic secretion through the nervous system in rats (Anini et al. 2000) and stimulate the endocrine pancreas to secrete insulin, somatostatin, and glucagon (Baldissera et al. 1988, Schjoldager et al. 1988,
GLP1R-β-arrestin 1/c-Src in INS832/13 cells (Talbot et al. 2009, 2012). The authors suggested that GLP1R/GCGR dual agonists may have inotropic and energy-preserving effects in insulin-resistant hearts and that these effects could be beneficial for the treatment of heart failure or cardiogenic shock in subjects with insulin resistance (Axelsen et al. 2012).

Renal effects
GLP1 agonists and DPP4 inhibitors cause moderate blood pressure lowering and lipid lowering in humans that may contribute to the reported cardiovascular benefits of this class of antidiabetic drugs (Mega et al. 2011, Liu et al. 2012, Panchapakesan et al. 2013). Glucagon causes natriuresis with changes in kidney sodium handling. Enhanced proximal tubular sodium reabsorption and a higher prevalence of hypertension have been associated with the Gly40Ser polymorphism of the GCGR gene resulting in a mutated receptor less responsive to glucagon (Strazzullo et al. 2001, Barbato et al. 2003). Consistently, a trend toward blood pressure increase was observed during pharmacological GCGR antagonism in T2D patients in a 4-week Phase IIa proof-of-concept study (Ruddy et al. 2011). No data so far have been published on the renal effects of OXM.

Neuroprotective effects
In preclinical studies, GLP1 agonists and DPP4 inhibitors (in association with GLP1 elevation) have been shown to counteract memory impairment, protect neurons from oxidative stress, and reduce plaque formation and the chronic inflammation response in the brains of mouse models of Alzheimer’s disease, Parkinson’s disease, and other degenerative diseases (Wu et al. 2003, D’Amico et al. 2010, Holscher 2012). GLP1R agonists are currently explored for the treatment of neurodegeneration (Mega et al. 2011, Liu et al. 2012, Panchapakesan et al. 2013), and glucagon has been recently reported to preserve neurological function following brain trauma in diabetic rats (Abu Fanne et al. 2011). No published reports so far have explored the effect of OXM or GLP1R/GCGR dual agonists on neuroprotection. The above studies suggest that simultaneous activation of the GLP1R and GCGR could result in potential beneficial effects in neurodegenerative disorders.

OXM, physiological or pharmacological role?
Because of the structural similarities of the proglucagon products, investigating the endogenous levels of OXM is difficult as ‘OXM-like immunoreactivity’ (OLI) has been estimated mostly using a two-step subtraction RIA or a RIA using an OXM C-terminal specific antibody (Blache et al. 1988). In the subtraction RIA, one assay is used to measure the concentration of total glucagon, using antibodies to the nonterminal epitopes of glucagon, which cross-react with glucagon, glicentin, and OXM (Fig. 2). A second assay is used to measure glucagon using antibodies to the exposed C-terminal of glucagon. To estimate OLI, the level of pancreatic glucagon is subtracted from the level of total glucagon (Kervran et al. 1987).

Using the OXM C-terminal octapeptide-specific antibody (Blache et al. 1988, Le Quellec et al. 1992), it was shown that, following i.d. administration of a meal, OLI raised in anesthetized rat plasma from 20.1 ± 2.7 to 176.1 ± 12.2 pmol/l at 30 min (Anini et al. 1999). Using the same RIA, Le Quellec et al. (1998) determined that fasting and meal-stimulated levels in healthy children were 71 ± 10 and 130 ± 26 pmol/l respectively and that the physiological 24-h OLI profile in human plasma shows a diurnal variation independent of food intake; the lowest levels were found in the early morning (~13.5 pmol/l) and the highest levels were found in the evening (~30.8 pmol/l) (Le Quellec et al. 1992). More recently, the subtraction RIA (Ghatei et al. 1983) has been used to estimate the OLI concentration in humans treated with OXM (Wynne et al. 2005). S.c. OXM (400 nmol preprandially) administered three times daily in overweight and obese subjects over a 4-week period resulted in...
a significant weight loss of 2.3 kg (Wynne et al. 2005). The endogenous fasting level of OLI was found to be 97.4±5.5 pmol/l, increasing to 116.5±10.4 pmol/l after a meal. OLI increased tenfold (972±165 pmol/l) 30 min after self-administration of OXM. These levels are similar to those found in gastrointestinal disease such as the levels reported in patients with tropical malabsorption (tropical sprue, approximately tenfold elevation vs normal patients) (Besterman et al. 1979), patients who have had small intestinal resection (Besterman et al. 1982), and following jejunal ileal bypass surgery (Holst et al. 1979, Sarson et al. 1981). The same authors using a similar experimental design and OXM administration demonstrated that 4-day s.c. self-administration of preprandial OXM (400 nmol) three times daily increased energy expenditure and decreased energy intake in overweight and obese volunteers (Wynne et al. 2006). The baseline plasma OXM levels were 41±7 pmol/l increasing to 63±16 pmol/l postprandially. When participants self-administered OXM, levels increased to 658±85 pmol/l immediately before the study meal (Wynne et al. 2006). Holst’s group using a different subtraction RIA to obtain OLI concentrations (Holst et al. 1976) reported fasting and postprandial plasma levels of 20–30 pmol/l (Falken et al. 2011).

The issues with the accurate quantification of OXM remain a confounder as a proportion of the OLI is represented by glicentin and different assays result in different readouts. Recently, Halquist et al. (2012) reported a two-dimensional reversed phase ion pair chromatography–tandem mass spectrometry approach for the analysis of OXM in rat plasma. This LC–MS method may provide new avenues of data that may not have been seen with other method platforms.

Based on the data available, it is unclear what the absolute values of OXM/OLI are in plasma during fasting and following a meal. It is, therefore, difficult to make conclusions about a potential physiological role of OXM. OXM shows similar functional potencies (EC_{50} cAMP production) at the GLP1R and GCGR (Baldissera et al. 1988, Gros et al. 1993, Holst 2000, Pocai et al. 2009, Kosinski et al. 2012) at ~1–2 orders of magnitude higher than the plasma levels of OXM/OLI reported in postprandial state and then only approach EC_{50} plasma levels when OXM is exogenously administered (Wynne et al. 2005, 2006). Based only on peripheral plasma OXM levels, it is unlikely that the endogenous levels of OXM result in physiological effects. More sophisticated technologies measuring the levels of OXM in critical sites such as the vagus or discrete brain-specific areas involved in the regulation of energy homeostasis are not readily available and are required to make any further conclusion. In these sites, the levels of OXM are anticipated to be higher in the postprandial state. Similarly, animal (Vahl et al. 2007) and human (Plamboeck et al. 2012) studies have demonstrated that an intact vagal innervation is important for the effect of GLP1 in the maintenance of glucose homeostasis. GLP1 is a substrate of DPP4 and is rapidly metabolized to GLP1 (9–37) or GLP1(9–36)NH2. DPP4, among other tissues and cell types, is found on the surface of endothelial cells of capillaries in the intestinal mucosa adjacent to the sites of GLP1 secretion (Hansen et al. 1999, Baggio & Drucker 2007). Consequently, <25% of newly secreted GLP1 enters the portal vein in intact form and only ~10–15% reaches the systemic circulation in the intact insulinotropic form where DPP4 also exists as a soluble form (Pridal et al. 1996, Mentlein 1999). OXM has a short half-life in circulation of ~12 min in humans (Schjoldager et al. 1988) and ~6 min in the rat (Kervran et al. 1990). It is removed by renal clearance and is a substrate of DPP4 (Zhu et al. 2003). Evidence of the involvement of DPP4 in the breakdown of OXM in vivo came from a study in which co-administration of OXM and a DPP4 inhibitor resulted in a greater reduction of food intake (Druce & Bloom 2006). The midsection of OXM may also be a target for degradative enzymes such as the ectopeptidases (Hupe–Södmann et al. 1997) and neutral endopeptidase 24.11 (NEP-24.11, nepriylin) (Hupe–Södmann et al. 1995, Deacon 2005, Plamboeck et al. 2005). This observation raised concerns regarding the relevance of portal GLP1 or other peptide concentrations in regulating glucose homeostasis and other pharmacodynamic effects and represents a potential limitation in the majority of studies that rely only on measurement of systemic levels of native peptides (Vahl et al. 2007).

Therefore, it is possible that the circulating active levels of OXM reflect, as in the case of GLP1, just a small portion of the secreted product and that the concentration at the site of secretion in the gut or brain is sufficient to elicit physiological responses (Kervran et al. 1990). It is also possible that additional receptors are involved in the action of OXM or that OXM acts synergistically when secreted together with other peptides (Field et al. 2010) recapitulating the post-Roux-en-Y gastric bypass situation (Ashrafian et al. 2011, Jørgensen et al. 2012). The understanding of the role of OXM as a potential physiological regulator of appetite and energy expenditure would be strengthened by the identification of a specific OXM receptor, by studies employing specific OXM antagonists or immuno-neutralizing antibodies that block the effects of OXM, but not glucagon or GLP1, or with genetic mouse models.

Therapeutic potential

The only treatments to date that produce lasting weight reduction are gastric banding and gastric bypass surgery, although the associated risk and costs limit their use. Patients that undergo gastric bypass have alterations of several signals that may contribute to their reduced appetite and enhanced glucose homeostasis. Among the changes consistently observed following RYGB are an exaggerated postprandial increase in OXM, glucagon, PYY, and GLP1 (Chandarana & Batterham 2012). Administration of endogenous gut peptides or more metabolically stable analog represents a potential long-term therapeutic approach to obesity and diabetes. OXM administered three times a day preprandially was demonstrated to reduce body weight in humans.
of fully activating both GLP1R and GCGR, improved glycemic control without body weight gain in db/db mice when combined with long-acting insulin (Fosgerau et al. 2011). Recently, Zealand Pharma announced the starting of a Phase 1 development of ZP2929 for the treatment of T2DM and/or obesity (Diabetes.co.uk, Sep 14, 2012) and Transition Therapeutics confirmed in a press release the completion of a Phase 1 study with TT-401, a weekly GLP1R/GCGR dual agonist developed for the treatment of diabetes (www.transitiontherapeutics.com/media/news.php, June 6, 2012).

**Conclusion**

Several trials have clearly demonstrated that lifestyle interventions (UKPDS 1995) and T2DM therapies such as sulfonylureas, metformin, and TZD result in progressive deterioration of glycemic control in T2DM patients associated with β-cell decline (Kahn et al. 2006). Therefore, restoration of insulin secretion and β-cell mass and function is a critical goal of future diabetes treatments. Thus far, incretin-based therapies (GLP1R agonists and DPP4 inhibitors) are providing durable glycemic control with improved insulin resistance and β-cell function (Klonoff et al. 2008, Derosa & Maffioli 2012, Derosa et al. 2012a,b, van Engen et al. 2012).

With these initial promising results from incretin mimetics and incretin enhancers, the next generation of diabetes drugs will likely focus on the alternate delivery for injectables (Owens 2002, Lee et al. 2009, Sloop et al. 2010) and the combined activation of more than one receptor. Simultaneous activation of GLP1R and GCGR with chimeric peptides and in the future nonpeptide orally available GLP1R/GCGR dual agonists is a conceivable option to achieve improved therapeutic goals. It will be critical to deepen our understanding of the mechanism of action and how structurally related peptides like GLP1 and glucagon interact with their respective receptors. Understanding of receptor oligomerization, heteromerization, and binding cooperativity will allow an improved understanding of how ligands should be designed to maximize the simultaneous activation of these complexes (Roed et al. 2012, Schelsborn et al. 2012, Whitaker et al. 2012). Finally, characterization of the post-receptor signaling of these closely related GPCR in the glucagon family will allow a better understanding of the pathways that need to be selectively modulated to achieve the desired effect while avoiding others responsible for undesirable adverse effects.

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