

THEMED ISSUE REVIEW

Glucagon-like peptide-1 in diabetes care: Can glycaemic control be achieved without nausea and vomiting?

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Introduced less than two decades ago, glucagon-like peptide-1 receptor agonists rapidly reshaped the field of Type 2 diabetes mellitus (T2DM) care by providing glycaemic control in tandem with weight loss. However, FDA-approved GLP-1 receptor agonists are often accompanied by nausea and emesis and, in some lean T2DM patients, by undesired anorexia. Importantly, the hypophagic and emetic effects of GLP-1 receptor agonists are caused by activation of central GLP-1 receptors. This review summarizes two different approaches to mitigate the incidence and severity of nausea and emesis related to GLP-1 receptor agonists: conjugation with vitamin B₁₂, or related corrin ring-containing compounds ('corination'), and development of dual agonists of GLP-1 receptors with glucose-dependent insulinotropic polypeptide (GIP). Such approaches could lead to the generation of GLP-1 receptor agonists with improved therapeutic efficacy, thus decreasing treatment attrition, increasing patient compliance and extending treatment to a broader population of T2DM patients. The data reviewed show that it is possible to pharmacologically separate the emetic effects of GLP-1 receptor agonists from their glucoregulatory action.

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KEYWORDS

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1 | INTRODUCTION

1.1 | Type 2 diabetes mellitus is a global health problem, and pharmacological intervention requires refinement to increase tolerability for patient quality of life in disease management

Diabetes is one of the most common chronic diseases in the world. According to the International Diabetes Federation (IDF), the incidence of diabetes has tripled over the last 20 years, reaching a prevalence of nearly

Abbreviations: AP, area postrema; B12, vitamin B12; Cbi, cobinamide; CDT, 1,1-dicarbonyl-di-(1,2,4-triazole); CeA, central nucleus of the amygdala; DMV, dorsal motor nucleus of the vagus; DPP-4, dipeptidyl peptidase-4; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HC, haptocorrin; IF, intrinsic factor; NTS, nucleus tractus solitarius; PBN, parabrachial nucleus; PPG, proglucagon; T2DM, type 2 diabetes mellitus; TC, transcobalamin.

10% among adults today (www.idf.org). Of the different forms of diabetes, Type 2 diabetes mellitus (T2DM) is the most prevalent form and accounts for the vast majority (~90%) of the total diabetic population (Saeedi, Petersohn et al., 2019). T2DM is a progressive metabolic disorder characterized by hyperglycaemia and deterioration in beta-cell function, paradoxically accompanied by defective insulin action due to the development of insulin resistance (Nauck & Meier, 2016). The global prevalence of the disease is increasing rapidly, largely due to concomitant increases in obesity (Leitner et al., 2017), as clear underlying mechanistic comorbidities exist between these two pathologies. Unfortunately, lifestyle interventions alone (i.e., diet and exercise-based interventions) are largely ineffective, in part due to poor adherence/compliance but also due to evolutionary metabolic mechanisms that intrinsically prevent sustained weight loss (Grill, 2020) and obfuscate T2DM management tools.

In the last few decades, many families of hypoglycaemic drugs have been developed for the treatment of T2DM such as synthetic insulin, **metformin**, **dipeptidyl peptidase-4 (DPP-4)** inhibitors, **sodium/glucose cotransporter-2** inhibitors and glucagon-like peptide-1 (**GLP-1**) analogues (American Diabetes Association, 2020; Buse et al., 2020; Lovshin & Drucker, 2009). Despite cases of remarkable success, all these drugs have been characterized by pitfalls and side effects that limit efficacy and narrow therapeutic windows, requiring intensified research efforts to fully manage T2DM (McGovern et al., 2018; Thrasher, 2017). Second-generation **GLP-1 receptor** agonists have now been approved by the Food and Drug Administration (FDA) for the treatment of T2DM. The development and marketing of **albiglutide**, **dulaglutide** and **semaglutide** have been extensively discussed and reviewed elsewhere (Avgerinos et al., 2020; Grill, 2020; Jendle et al., 2016; Madsbad, 2016; Rendell, 2018; Sharma et al., 2018). In this review, we highlight recent advances in the development of promising GLP-1 receptor agonist-based approaches that have not yet received FDA approval and will describe the underlying mechanisms identified in preclinical studies, discussing potential translational relevance of these novel pharmacotherapies with special emphasis on 'in-built' strategies to mitigate the most prominent side effects of the GLP-1 receptor agonists, such as nausea and vomiting. Specifically, we discuss the advantages of GLP-1 agonism in conjunction with glucose-dependent insulinotropic polypeptide (**GIP**), and GLP-1 conjugation with vitamin B₁₂ (B12) as potential future strategies to mitigate or eliminate the side effects characteristic of current GLP-1 receptor agonists.

1.2 | The GLP-1 system and the history of GLP-1 analogues: *Remarkable control of glycaemia, if tolerated*

The search for insulin-stimulating factors (the incretins) began over 100 years ago in the hopes of uncovering endogenous peptides with potential hypoglycaemic utility (Kim & Egan, 2008). GLP-1 is a multifaceted hormone with broad pharmacological potential (Drucker, 2018). First isolated in 1986 from the gut, GLP-1 has since been found to both stimulate insulin secretion and inhibit glucagon release (Drucker et al., 2017). Together with GIP, these two proteins are the only two known endogenous incretins (Holst, 2019). Glucose-stimulated insulin secretion by GLP-1 is only one of the beneficial

effects for T2DM management. Other known GLP-1 effects on metabolism that are relevant to T2DM include the slowing of gastric emptying, inhibition of food intake and modulation of beta-cell proliferation (Holst, 2007; Muller et al., 2019; Rowlands et al., 2018).

GLP-1 is a post-translational product of the peptide proglucagon (PPG) expressed in the enteroendocrine L cells of the small intestine and in pancreatic alpha-cells (Eissele et al., 1992; Kauth & Metz, 1987). Within minutes of the ingestion of nutrients, GLP-1 is released by enteroendocrine L cells (Jorsal et al., 2018). However, due to rapid degradation by the enzyme DPP-4, only ~10% of endogenously released GLP-1 reaches the systemic circulation (Muller et al., 2019). PPG is also expressed centrally, primarily in the nucleus tractus solitarius (NTS) (Merchenthaler et al., 1999) of the caudal brainstem, an integrative relay nucleus for satiety and emetic signals controlling ingestive and malaise behaviour (Grill & Hayes, 2012). GLP-1-expressing NTS neurons project to various GLP-1 receptor-expressing nuclei throughout the CNS (Llewellyn-Smith et al., 2011) implicated in the control of food intake and energy balance (Dunphy et al., 1998; Merchenthaler et al., 1999). Central administration of GLP-1 or GLP-1 receptor agonists reduce food intake and body weight, reproducing the effects of systemically delivered GLP-1 receptor agonists (Alhadeff et al., 2016; Barrera et al., 2011; Hayes et al., 2010; Turton et al., 1996) and highlighting a predominant role of the central GLP-1 system in the regulation of feeding.

As a treatment for the management of metabolic diseases, native GLP-1 has proven largely ineffective as a pharmacotherapy due to the necessity for repeated, large doses to overcome the extremely short half-life, ~2 min, due to degradation by DPP-4 (Muller et al., 2019). Nearly 30 years ago, it was discovered that a compound extracted from the salivary gland secretions of the Gila monster has similar properties to human GLP-1, which led to the development of the peptide **exendin-4** and its synthetic form, exenatide (Eng et al., 1992). Exendin-4 exhibits a modified amino acid sequence, relative to human GLP-1, thereby allowing the compound to be remarkably resistant to enzymic degradation by DPP-4 and extending its half-life to ~2.5 h (Copley et al., 2006; Kieffer et al., 1995). In 2005, exenatide became the first FDA-approved GLP-1 analogue for the treatment of T2DM. Shortly after, in 2008, exendin-4 was approved by the European Medicines Agency (EMA) for the treatment of obesity (Davidson et al., 2005). The entry of exendin-4 into the T2DM landscape was followed in 2009 by **liraglutide**, an acylated (i.e., lipidated) and DPP-4-resistant GLP-1 analogue derived from human GLP-1 (Nauck & Meier, 2019), which was approved by the FDA for the treatment of obesity in 2014 (Muller et al., 2019). In doing so, exendin-4 and liraglutide became the first glucose-lowering medication options for reducing body weight, according to FDA/EMA standards, thus providing additional health benefits for the overweight T2DM patient population. With advances in biotherapeutic engineering, studies focused on exendin-4 and liraglutide inspired drug discovery campaigns over the subsequent two decades to deliver 'second-generation' GLP-1 receptor agonists for treating T2DM, most notably **albiglutide**, **dulaglutide** and **semaglutide** (Williams et al., 2020). These developments yielded substantial overall

metabolic improvements in patients compared with the first-generation GLP-1 receptor agonists that include superior and longer lasting hypoglycaemic actions and greater body weight loss. However, these compounds were still plagued by a high incidence of side effects, mostly of gastrointestinal (GI) nature, such as nausea and vomiting (Ahren et al., 2018; Bettge et al., 2017; Pratley et al., 2018).

1.3 | Nausea and emesis are the most common side effects of *all* existing GLP-1-based therapies and limit T2DM management

The 13th US Surgeon General, C. Everett Koop, famously stated, ‘Drugs don’t work in patients who don’t take them’, encapsulating an important segment of T2DM patients and challenges to treatment adherence over time. Current GLP-1 receptor agonists are extraordinary medicines but importantly are not immune to pitfalls characterized by all-too-common side effects such as GI distress, nausea, vomiting and diarrhoea (Bettge et al., 2017; Filippatos et al., 2014). These side effects occur in a dose-dependent manner, which generally limits the use of higher doses to drive satisfactory glycaemic control and proper disease management. Evidence-based medical reports are now clear that nausea and emesis are the principal reported side effects of existing GLP-1-based therapeutic agents (Bettge et al., 2017). A recent report from GlaxoSmithKline concluded that ‘Patients reported that GI-related issues “Made me feel sick” (64.4%) and “Made me throw up” (45.4%) as their top reasons for discontinuation’ (Sikirica et al., 2017). The same report showed ‘disparities between patient experiences and physician perceptions’ and suggested major ‘gaps in physician–patient communication’ regarding GLP-1-therapeutic agents and incidence of illness. Indeed, it has been reported for decades in the cancer literature that physicians and nurses vastly underestimate incidence of nausea and emesis in outpatient settings (Aapro, 2018). Additionally, the documentation of these side effects in clinical trials is often via self-reporting rather than validated, structured and homogenized questionnaires, which further complicates assessments and between-study comparisons. Report after report for every GLP-1 based therapeutic agent reads with incidence of nausea and emesis warranting strategies for improvement (see Bergenstal et al., 2010; Bettge et al., 2017; Buse et al., 2004; John et al., 2007; Jones et al., 2018; Kendall et al., 2005; Lean et al., 2014; Nauck et al., 2016; Ratner et al., 2010). These effects are not transient nor insignificant as they lead to discontinuation of treatment in ~6–10% and reduced dose tolerance in another ~15% of T2DM patients (Bergenstal et al., 2010; Buse et al., 2004; Capehorn et al., 2020; John et al., 2007; Kendall et al., 2005; O’Neil et al., 2018; Trujillo, 2020). To put this major issue into a different set of numbers demonstrating the magnitude of this problem, approximately one in four T2DM patients (~6.5 million US citizens) are prevented from the full benefit of current FDA-approved GLP-1-based therapeutic agents, and up to 50% of patients (~13 million Americans) that may be prescribed an existing GLP-1-based therapeutic agent will experience nausea and emesis. These statistics together support the notion that

future GLP-1 receptor agonists designed to eliminate nausea and emesis have a high therapeutic potential for T2DM patients.

Any strategy addressing emesis and emetic behaviour improvements must consider that the vomiting response is largely controlled by an emetic centre located in the brainstem (Babic & Browning, 2014; Baker et al., 2005; Hesketh, 2008; Horn, 2014; Miller & Leslie, 1994). This anatomical emetic ‘hub’ is composed of three distinct nuclei—the NTS, the adjacent dorsal motor nucleus of the vagus (DMV) and the area postrema (AP). Physiological and pathological modulators of energy balance share many common neural substrates and anatomical nodes within the brain including the AP/NTS (Babic & Browning, 2014; Hesketh, 2008; Miller & Leslie, 1994). The AP/NTS is the primary target of vagal afferent projections originating from the gut. Additionally, the presence of fenestrated capillaries allows neurons in the AP/NTS to be easily reached by circulating emetic/anorectic agents that cannot readily cross the blood–brain barrier (Miller & Leslie, 1994; Price et al., 2008). Increased neuronal activity in the AP/NTS is associated with emesis and nausea (Baker et al., 2005). Importantly, virtually, all existing approved GLP-1 analogues, as well as other emetic stimuli, such as the highly emetogenic chemotherapeutic agent cisplatin, activate neurons in the AP/NTS and upstream CNS targets implicated in the regulation of not only feeding behaviour but also in the development of aversion and illness behaviours, such as the parabrachial nucleus (PBN) and the central nucleus of the amygdala (CeA) (Alhadeff et al., 2017; Baraboi et al., 2011; De Jonghe & Horn, 2009; Gabery et al., 2020; Salinas et al., 2018). Direct activation of the GLP-1 receptors expressed in various nuclei of the CNS reproduces the body weight and food intake suppressive effects, as well as the behavioural signs of malaise observed following systemic administration of GLP-1 receptor agonists (Kanoski et al., 2011; Kanoski et al., 2012; Mietlicki-Baase et al., 2018; Secher et al., 2014; Sisley et al., 2014).

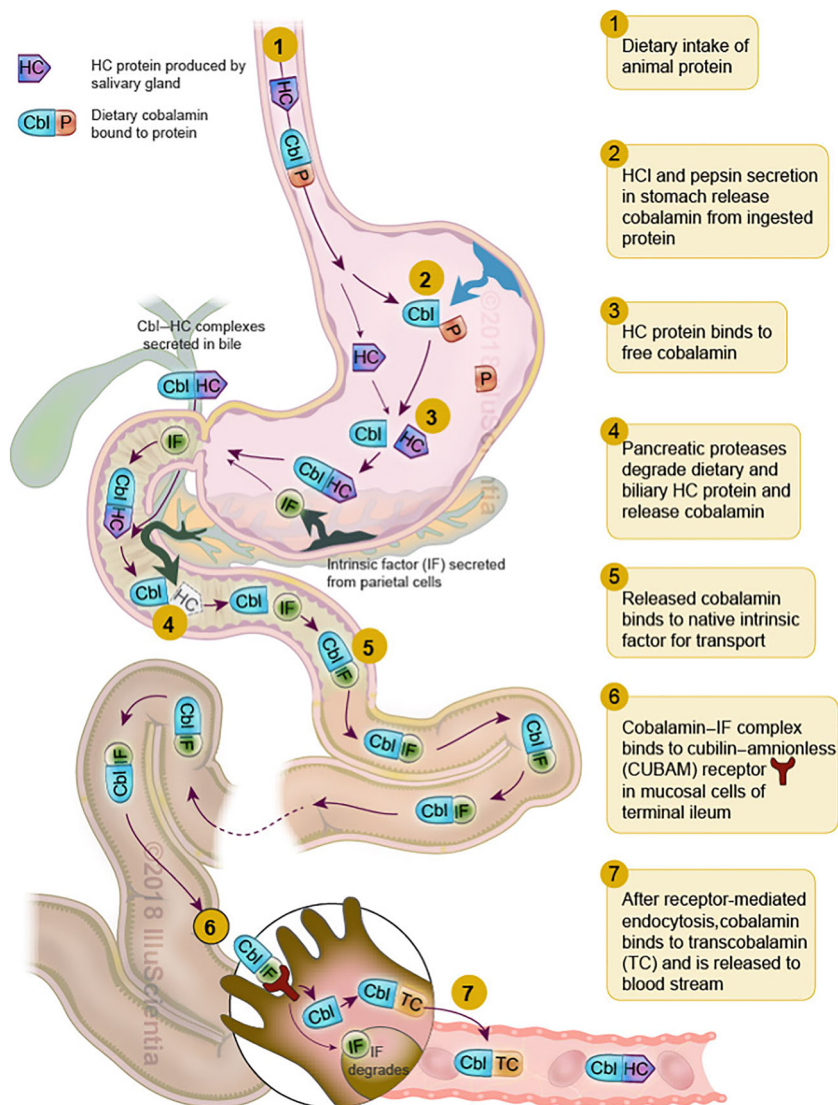
Despite the enhanced half-life (i.e., sustained agonism) and the use of titration schemes to slowly increase drug levels as a means to reduce some side effects (Nauck & Meier, 2019), significant attrition due to intolerance to GLP-1 pharmacotherapy has and continues to occur mainly due to reported GI side effects. Thus, considering the dose-limiting side effects, there is a clear clinical need for safer and more effective GLP-1-based analogues. In this review, we discuss the advantages of GLP-1 agonism in conjunction with GIP, as well as GLP-1 conjugation with corrin ring-containing molecules such as vitamin B12 (B12) or cobinamide (Cbi).

2 | CONJUGATION WITH B12 AND Cbi: ALTERING PHARMACODYNAMICS TO PREVENT GLP-1 RECEPTOR-INDUCED EMESIS AND NAUSEA

2.1 | General vitamin B12 physiology

Coined ‘nature’s most beautiful cofactor’ due to its deep red colour, B12 is the largest and most complex of all vitamins and one of nature’s rare organometallic compounds. B12 is a water-soluble

FIGURE 1 Schematic representation of the dietary uptake pathway of vitamin B12 in humans. Cbl, cobalamin/B12; HC, haptocorrin; IF, intrinsic factor; P, protein



molecule that is critical for red blood cell formation, proper neurological function, and DNA and protein synthesis (Nielsen et al., 2012). Because B12 can only be synthesized by bacteria, mammals (including humans and rats) must ingest the vitamin for survival as an essential nutrient. A highly efficient system for the absorption and cellular uptake of B12 exists (see Figure 1 and Green et al., 2017). Once B12 is released in the gastric lumen, the glycoprotein haptocorrin (HC) binds it, protects it from the stomach's low pH and carries it to the duodenum (Morkbak et al., 2007), where HC is then degraded and B12 is free to bind another glycoprotein, the intrinsic factor (IF) (Allen et al., 1978; Gordon et al., 1991). This IF transports B12 through the intestine into the terminal ileum, where the IF-B12 complex undergoes receptor-mediated endocytosis into the ileal enterocyte (Birn et al., 1997; Fyfe et al., 2004; Kozyraki et al., 1998). In the cytoplasm of the ileal absorptive cells, B12 becomes bound to transcobalamin (TC), which mediates its secretion into the blood plasma and carries it to cells that require B12 (Russell-Jones & Alpers, 1999).

2.2 | The B12 corrination technology

The structural heart of B12 is a corrin ring: a 19-carbon, asymmetric, mono-protonated, tetrapyrrole ring system with a centrally coordinated cobalt atom (Co^{3+}). This structure allows for multiple areas that can be chemically modified and/or conjugated to other moieties. However, maintaining recognition of B12 by its key transport proteins is critical but can be achieved through select modification of, and/or conjugation to, B12. Several modifications of B12 have been published, including those at the amide side chains, the phosphate group, the cobalt centre or the ribose secondary hydroxyl group (Figure 2) (ó Proinsias et al., 2013). Our team has successfully generated, validated and characterized several peptide conjugates, such as those with insulin (Petrus et al., 2007), PYY₃₋₃₆ (Fazen et al., 2011) and GLP-1 (Clardy-James et al., 2013) at the 5'-OH position (see Table 1). This site was previously shown to be reactive in a coupling reaction with 1,1-dicarbonyl-di-(1,2,4-triazole) (CDT) coupling agent, and such conjugates retained binding with IF and TC (Fedosov et al., 2006).

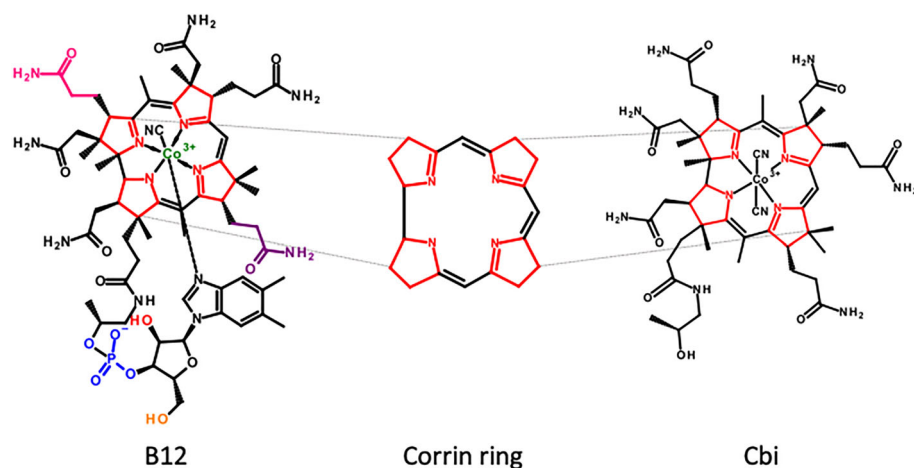


FIGURE 2 Schematic representation of vitamin B₁₂ (B12), corrin ring (shown deprotonated) and dicyanocobinamide (Cbi). ‘Corrination’ is derived from the use of corrin ring-containing molecules such as Cbi or B12

TABLE 1 List of corrinated peptides tested in the context of energy balance and diabetes preclinical models

Corrination moiety	Peptide/protein	In vivo model	Mode of administration	Key outcomes	Reference
B12	Insulin	Rat	Oral	Prolonged hypoglycaemic activity and increased half-life	(Petrus et al., 2007)
B12	Ex4	Rat Mouse Shrew	s.c., i.p. and i.c.v.	Maintained glucoregulation, no effect on food intake and body weight, and near absence of emetic events	(Borner, Shaulson, et al., 2020; Mietlicki-Baase et al., 2018)
B12	PYY ₃₋₃₆	Rat	s.c.	Augmented hypophagia and weight loss	(Henry et al., 2015)
IF-B12	Ex4	Not tested	Not applicable	Increased gut and kidney protease resistance	(Bonaccorso et al., 2015)
Cbi	Ex4	Rat Shrew	i.p.	Improved glycaemic response in IPGTT and reduction of emetic events	(Borner, Workinger, et al., 2020)

Abbreviations: B12, vitamin B₁₂; Cbi, cobinamide; Ex4, exendin-4; IF, intrinsic factor; IPGTT, intraperitoneal glucose tolerance test.

Successful conjugation strategies utilized for the improvement of GLP-1 have focused on the use of lipidation and conjugation to antibody fragments. Dulaglutide, developed by Eli Lilly, successfully conjugated GLP-1 (7–37) to an Fc fragment of IgG4. The use of fatty acid GLP-1 conjugates is highlighted by liraglutide and semaglutide—compounds developed by Novo Nordisk. An additional conjugation strategy, although less explored, is corrination; the use of B12 or any of its biosynthetic corrin-containing precursors (e.g., dicyanocobinamide [CN₂Cbi]) (Figure 2), with the aim of altering pharmacology. Although exendin-4 readily penetrates the CNS (Kastin & Akerstrom, 2003; Mietlicki-Baase et al., 2018), less is known about the penetrance of B12 into the adult brain (Kanazawa & Herbert, 1983). Uptake of B12 into the brain is likely to be a receptor-mediated process with megalin, a receptor capable of TC–B12 uptake, being expressed in the choroid plexus (Carro et al., 2005). Additional evidence points to the importance of the CD320 receptor, as well as the transmembrane protein, amnionless (Luder et al., 2008). Collectively, this information points to a receptor-mediated process of B12 blood–brain barrier penetrance. It is, however, clear that in the adult brain with limited neurogenesis, uptake of B12 by the CNS is very low and considerably lower than in other organs, especially the liver and

kidney (Ikotun et al., 2014; Sah et al., 2014). A recent study using radioactively labelled B12 (B12-⁸⁹Zr) reveals less than 0.1% injected dose per gram (ID·g⁻¹) of B12 in brain in mouse models with over 5% ID·g⁻¹ observed in pancreas (Kuda-Wedagedara et al., 2017). Importantly, evidence collected *post-mortem* from human brain and liver clearly demonstrates negligible amounts of B12 (11.3 pmol·g⁻¹) and a ~10-fold lower relative concentration of corrinoid-type analogues (1.3 pmol·g⁻¹; including Cbi) in the brain, with the liver being the main site of concentration for both B12 and corrinoid analogues (total >600 pmol·g⁻¹) (Kanazawa & Herbert, 1983).

Overall, from a therapeutic perspective aimed at normalizing the chronic hyperglycaemia of T2DM patients, designing a GLP-1 receptor agonist that does not penetrate readily into the CNS, but retains enhanced pharmacological action on beta cells, would theoretically provide an improved tool for glycaemic control without eliciting unwanted nausea/malaise and/or anorexia. Corrination has been utilized to deliver several bioactive and/or imaging molecules, ranging from ^{99m}Tc to insulin (see Table 1). The conjugation of peptides to corrins offers a unique delivery system of peptides through the B12 uptake pathway. Unlike other conjugation strategies, corrination increases the hydrophilicity of the peptide and thus increasing

solubility, a common limitation to peptide therapeutic agents. The use of corrins for conjugation to peptides and other low MW compounds has been well explored, and their synthesis is simple and direct. As an additional benefit, corrination has also been shown to be successful at limiting proteolytic degradation of exendin-4 (Bonaccorso et al., 2015).

2.3 | In vitro and in vivo characterization of B12-exendin-4: Do conjugates with reduced brain penetrance reduce GLP-1-induced nausea and vomiting?

Initial in vitro screenings demonstrated that covalent conjugation of the GLP-1 receptor agonist exendin-4 to B12 between the vitamin 5-OH group and the K12 position of exendin-4 retains potent agonism (68 pM) of the GLP-1 receptor, either as the free conjugate or bound to the critical transport protein for B12 absorption IF (126 pM), confirming the ability of B12-exendin-4 to interact with both systems. Results of in vivo evaluation of the effects of systemic B12-exendin-4 and unconjugated exendin-4 on food intake and body weight, glucose tolerance and in the development of taste avoidance (CTA, an assay of illness behaviour) in rodents showed that the B12-exendin-4 conjugate improved glucose tolerance but did not elicit CTA and anorexia produced by unconjugated native exendin-4 (Mietlicki-Baase et al., 2018). Follow-up studies also showed that the B12-exendin-4 enhanced glucose clearance, relative to exendin-4 and similar to liraglutide in Goto-Kakizaki (GK) rats, a lean, polygenetic model of T2DM (Goto et al., 1976; Ostenson & Efendic, 2007), but did not produce the CNS-dependent outcomes of anorexia and body weight loss characteristic of these two compounds (Borner, Shaulson, et al., 2020). Rats treated with native exendin-4 exhibit an acute hyperglycaemic response, a phenomenon tied to the high CNS penetrance of exendin-4 and commonly observed across different rat models (Gao & Jusko, 2011; Perez-Tilve et al., 2010). Conversely, B12-exendin-4 did not produce a transient stress-induced hyperglycaemic in lean healthy and GK diabetic rats (Borner, Shaulson, et al., 2020; Mietlicki-Baase et al., 2018). To further evaluate whether differences in the effect profiles of B12-exendin-4 and unconjugated exendin-4 are the result of altered CNS penetrance, rats received systemic injections of fluorescein-exendin-4 (Flex), Cy5-B12 or Cy5-B12-exendin-4, and brain penetrance was evaluated using confocal microscopy. Although Flex robustly penetrates the brain (dorsal vagal complex and paraventricular nucleus of the hypothalamus), Cy5-B12 and Cy5-B12-exendin-4 fluorescence were not observed centrally, supporting a lack of CNS penetrance into these regions of the brain, in line with observed reduction in CNS-associated side effects of exendin-4. However, Cy5-B12-exendin-4 colocalized with insulin in the pancreas, suggesting direct pancreatic action as a potential mechanism underlying the hypoglycaemic effects of B12-exendin-4 (Mietlicki-Baase et al., 2018).

To definitively address the question of whether B12 conjugation would prevent emesis induced by exendin-4, the musk shrew (*Suncus*

murinus) was used to evaluate the in vivo efficacy and tolerability of B12-exendin-4. In contrast to rodents, shrews are capable of emesis (Ueno et al., 1987) and are believed to have a nearly identical B12 binding profile in blood as humans (71% amino acid sequence identity to human HC in *Tupaia chinensis* [Chinese tree shrew], Accession No. XP_006147468.1). Importantly, in the context of modelling the GLP-1 system, previous studies conducted by John Rudd and his research team amply demonstrated the ability of existing GLP-1 receptor agonists to induce hypoglycaemia, anorexia and emesis in this model (Chan et al., 2011, 2013). In line with the rodent data, all exendin-4 doses tested induced anorexia and body weight loss in shrews, but no such effects occurred after B12-exendin-4, even at suprapharmacological doses (Borner, Shaulson, et al., 2020). Importantly, B12-exendin-4 administration at $\sim 10\times$ the effective dose necessary for glucoregulation did not cause emesis compared with the potent emetic effects of exendin-4 that were observed in all animals tested (Borner, Shaulson, et al., 2020). Additional evidence showing that B12-exendin-4 induced profound emesis when administered centrally (i.e., direct CNS stimulation) further validates the thesis of an altered pharmacodynamic profile of the corrinated peptide.

2.4 | The B12 precursor dicyanocobinamide (Cbi) as an alternative to B12

Cbi, a corrinated precursor of B12, has been identified in humans (Hardlei & Nexø, 2009) but has no known influence on normal B12 homeostasis because it is not recognized by the B12 blood-transporting protein TC, critical for blood-brain barrier penetrance and cell entry via the CD320 receptor (Green et al., 2017; Luder et al., 2008). Instead, Cbi is recognized in the blood *only* by the B12-binding protein HC. The function of circulating HC is unknown, and no known specific receptor for the Cbi-HC complex has been identified (Furger et al., 2012). Congenital defects in plasma HC are asymptomatic, suggesting that HC and Cbi are not physiologically relevant in humans (Rosenblatt et al., 2001). The theoretical major advantage of the Cbi-exendin-4 construct over the B12-exendin-4 is that by using Cbi as a pharmacodynamic/pharmacokinetic modifier of a target peptide pharmaceutical agent, one can generate an 'inert' carrier that does not alter B12 homeostasis. This is especially relevant for possible future applications in humans over chronic use (as it would be the case for T2DM patients), as there is a very limited, albeit possible, outcome where B12-exendin-4 could interfere with the normal B12 physiology, potentially causing pernicious anaemia. This risk is completely avoidable by using Cbi, as it is only recognized by HC, and not by TC. A library of corrinated constructs of exendin-4 were synthesized by introducing two specific conjugation sites (at position K12 and K40) into the exendin-4 amino acid sequence and using various linkers with diverse chemical properties including hydrophobicity, amphiphilicity and rigidity (Borner, Workinger, et al., 2020; Tinsley et al., 2021). Two optimized conjugates were subsequently assayed *ex vivo* for GLP-1 receptor-binding in HEK-239 cells stability

transfected with hGlp1r and for insulin secretion in rat islet cells (Borner, Workinger, et al., 2020; Tinsley et al., 2021). Functional agonism screening revealed EC_{50} values between ~ 10 and 200 pM for the Cbi-exendin-4 conjugates, thus effectively proving the successful generation of compounds with agonist activity comparable to that of than native exendin-4. Using radio- ^{57}Co -B12 binding assays and serum B12 protein isolation, the presence of both HC and TC in shrew blood was confirmed (Borner, Workinger, et al., 2020). Subsequent ELISA-based pharmacokinetic studies in shrews showed that Cbi-exendin-4 exhibited reduced plasma clearance relative to native exendin-4, most likely due to improved stability of the conjugate to proteolytic activity, as previously demonstrated for B12 conjugates (Bonaccorso et al., 2015), and/or reduced renal clearance, both key factors in determining the half-life of exendin-4 in vivo (Copley et al., 2006; Simonsen et al., 2006). Similar to what was performed for the B12-exendin-4 conjugate, as a first validation in vivo, it was tested in shrews whether Cbi-exendin-4 retained ability to reduce blood glucose following an intraperitoneal glucose tolerance test (IPGTT), across a wide dose range. At all doses tested, similar enhanced glucose clearance actions of Cbi-exendin-4 and exendin-4, compared with vehicle, were observed, indicative of a comparable glucoregulatory potency (Borner, Workinger, et al., 2020). It is likely that Cbi-exendin-4 may also retain pharmacological actions for a longer duration compared with the native peptide as Cbi-exendin-4, but not native exendin-4, effectively suppressed plasma glucose concentrations following an IPGTT 6 h after drug administration. Extensive dose-response studies were conducted analysing the effects of Cbi-exendin-4 on various aspects of feeding behaviour (food intake and body weight emesis) in shrews. Overall, the outcome of these studies was similar to results with B12-exendin-4 (Borner, Workinger, et al., 2020), highlighting that Cbi can be leveraged for the generation

of active corrinated compounds as shown previously for B12 constructs, which can improve glycaemic control without producing anorexia and drug treatment-induced malaise but without the risk of causing alteration in the physiological B12 system.

By exploiting a B12 or its precursor Cbi, it is possible to generate potent and metabolically stable GLP-1 receptor agonists via 'corrination', with enhanced and prolonged peripheral glucoregulatory action minimal effects on feeding and without emesis and nausea (see Figure 3). The striking difference in occurrence and severity of nausea and emesis described here is likely to be attributable to reduced penetration of the corrinated constructs due to the presence of the highly polar nature of Cbi or B12 and the lack of an active transport mechanism into the adult brain. Consequently, this translates into a reduced activation of central GLP-1 receptors, including those located in the AP/NTS, the activation of which is key for the induction of emesis/nausea following GLP-1 receptor agonist treatment. Although longitudinal animal studies, as well as clinical trials, are needed to evaluate the long-term efficacy and tolerability of the corrinated exendin-4s, these preclinical data highlight the translational potential of the corrination technology in the context of GLP-1 receptor agonists.

3 | DUAL GLP-1 RECEPTOR AGONISTS

Dual agonism via a peptide-peptide conjugate or chimeric co-agonism has several advantages often translating to improved clinical utility compared with the administration of individual single active peptides in combination, including a singular pharmacokinetic and pharmacodynamic profile (e.g., affecting rates of absorption, distribution and half-life). In recent years, inspired by the early successful outcomes of GLP-1/glucagon (Gcg) co-treatment as a means to increase weight

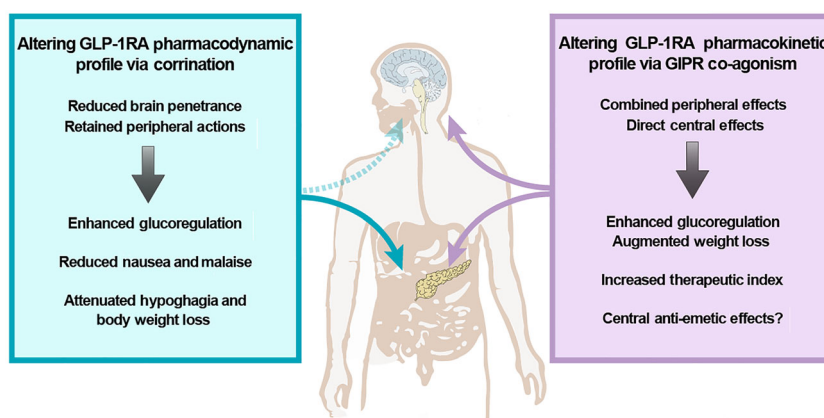


FIGURE 3 Main effects and mechanisms of vitamin B₁₂ (B12)/cobinamide (Cbi)-GLP-1 receptor agonist (GLP-1RA) and GIP receptor (GIPR)/GLP-1 receptor (GLP-1R) strategies. Corrination reduces brain penetration, radically changing the pharmacodynamic profile of GLP-1 receptor agonists. Corrinated GLP-1 receptor agonists retain a peripheral site of action when systemically administered, providing a pancreatic mechanism for GLP-1 receptor-mediated glycaemic control, without producing any centrally mediated illness-like behaviours (i.e., nausea and emesis). GIPR/GLP-1 receptor dual agonism enhances peripheral effects on glucose handling, while simultaneously decreasing feeding and body weight via direct central actions. Such a combinatorial approach offers valuable opportunity to increase the therapeutic window/index via dose modifications. Moreover, GIP receptor agonism may also antagonize GLP-1 receptor emetic signal(s) by engaging a yet unknown central mechanism(s) that could reduce the incidence and severity of nausea and emesis characteristic of current GLP-1 receptor-based approaches

loss in preclinical models (Pocai et al., 2009), several peptide hybrids quickly populated the pharmacological landscape including dual receptor agonists of GLP-1/Gcg (Ambery et al., 2018; Boland et al., 2020), GLP-1/GLP-2 (Wismann et al., 2018), GIP/GLP-1 (Coskun et al., 2018; Finan et al., 2013; Frias et al., 2017, 2018, 2020) and GLP-1 /**NPY-Y₂ receptors** (Chepurny et al., 2018; Milliken et al., 2021; Ostergaard et al., 2021). These dual agonists have been extensively reviewed elsewhere (Baggio & Drucker, 2020; Tschop et al., 2016). Their utility is currently being evaluated in the clinical setting, with the latter class being the most promising so far. Unfortunately, most of these studies did not include an exhaustive description of nausea and emesis side effects in humans and lack a proper in-depth investigation of nausea and emesis in preclinical models. Additionally, groups such as a 'classical' GLP-1 receptor agonist at doses matched for efficacy in body weight reduction or gluoregulatory effects were not included in many of the clinical trials. Therefore, interpretations regarding their ability to reduce nausea and emesis in humans and/or preclinical models, when matched for effect size in glucose regulation or body weight loss, are challenging.

3.1 | GIP/GLP-1 dual agonists, greater than the sum of their parts

GIP is a gut hormone released from the enteroendocrine cells in the duodenum and jejunum shortly after a meal (Baggio & Drucker, 2007). Together with GLP-1, GIP plays an important role in orchestrating the body's response to the increase of postprandial glucose levels by augmenting insulin secretion (Dupre et al., 1973; Fehmann et al., 1995; Muller et al., 2019). GIP binds to its receptor (**GIP receptor**), which is widely expressed throughout the body including in several areas of the brain involved in regulating energy balance, such as the hypothalamus and the caudal hindbrain (Adriaenssens et al., 2019; Kaneko et al., 2019). Although GLP-1 receptor agonists have been developed and employed with success for the treatment of T2DM and obesity, preclinical and clinical data regarding the potential use of GIP analogues are limited and controversial (see Finan et al., 2016; Samms et al., 2020). Compounds targeting the GIP receptor alone were initially abandoned due to an overall weak biological effect, in part because of early findings suggesting GIP resistance in diabetes (Nauck et al., 1993) alongside incongruent results on its hypophagic and body weight-lowering effects (Boylan et al., 2015; Finan et al., 2016; Killion et al., 2018; McClean et al., 2007; Miyawaki et al., 2002; Mroz et al., 2019). There is convincing evidence that the increase in glucose-stimulated insulin secretion following administration of exogenously applied GIP is mediated by direct activation of GIP receptors expressed on pancreatic beta cells (Baggio & Drucker, 2007; Khan et al., 2020), but the role of GIP receptors expressed within the CNS is less clear and only a few studies have investigated the central actions of GIP ligands on feeding behaviours (Ambati et al., 2011; Kaneko et al., 2019; NamKoong et al., 2017; Zhang, Delessa, et al., 2021). Recent studies using long-acting GLP-1/GIP receptor dual agonists, however, have yielded promising results in

preclinical models and clinical trials, providing greater body weight loss and better glycaemic control than GLP-1 receptor agonists alone (Coskun et al., 2018; Frias et al., 2017; Frias et al., 2018; Killion et al., 2018; Norregaard et al., 2018).

The first characterization of a dual GIP/GLP-1 receptor agonist was reported in 2013 via landmark publications in multiple preclinical models and human subjects (Finan et al., 2013; Frias et al., 2017). Using an approach that leveraged the high degree of homology between GIP and GLP-1 to generate hybridized GLP-1/GIP monomolecules, amino acids from native GLP-1 and GIP were introduced into the native glucagon sequence and the resulting peptides were screened for activity at the GLP-1 and GIP receptors (Finan et al., 2013). The final, unimolecular balanced dual agonist (NNC0090-2746/RG7697) was further modified to prevent DPP-4 degradation and to extend solubility (Finan et al., 2013). In two mouse models for T2DM (i.e., diet-induced obese and leptin-deficient mice), daily administration of this dual agonist reduced body weight, hyperglycaemia and dyslipidaemia (Finan et al., 2013). In cynomolgus monkeys, GIP/GLP-1 co-agonism was shown to be superior in reducing blood glucose levels and increasing plasma insulin, compared with equimolar doses of liraglutide (Finan et al., 2013). The dual agonist also decreased plasma insulin and decreased blood glucose during a glucose infusion challenge, more effectively than liraglutide, in healthy, nondiabetic human subjects. Collectively, these data highlight the translational potential of this class of drugs. Importantly, there was a reported reduction in the incidence of gastric-related adverse events for the co-agonist as compared with GLP-1 mono-agonist treatment (Finan et al., 2013). In subsequent clinical trials conducted by the same research team in healthy and T2DM patients, the same peptide and further optimized versions demonstrated high tolerability, dose-dependent reductions in fasting and postprandial plasma glucose, and reduced body weight, total cholesterol and leptin levels, relative to placebo controls (Frias et al., 2017). Together, these data clearly support the beneficial effects of targeting both incretin systems to provide enhanced effects, as well as to offer valuable opportunity of increasing the therapeutic window or index, via dose modifications (Finan et al., 2016; Samms et al., 2020) (see Figure 3).

3.2 | Central GIP receptor activation: Anti-emetic counteraction of GLP-1-induced emesis?

Activation of GIP receptors may have surprising anti-emetic effects, as recently described in a patent application filed by the pharmaceutical company Takeda (Asami et al., 2018). In these studies, GIP receptor agonists were capable of reducing CTA and emetic responses that usually occur following administration of the gut peptide PYY and cisplatin, in ferrets and beagles (Asami et al., 2018).

One can therefore speculate that GIP could not only potentiate the peripheral effects of GLP-1 receptor agonists on glucose handling but also antagonize GLP-1 receptor emetic signal(s) by engaging a yet unknown central mechanism(s) that ultimately reduces the incidence and severity of nausea and emesis characteristic of current GLP-1

receptor agonist-based approaches. The mechanism(s) and the circuitry engaged by GIP, in particular those underlying its anti-emetic actions, are lacking, despite recent work describing the phenotype of GIP receptor-expressing neurons in the various CNS nuclei involved in the control of energy homeostasis, including the AP and NTS (Adriaenssens et al., 2019; Ludwig et al., 2021; Zhang, Kaye, et al., 2021). In one of these studies, Zhang, Kaye, et al. (2021) generated the full transcriptome profile of each individual AP neuron via single-nuclei RNA sequencing of murine AP tissue. Intriguingly, a significant portion of the neurons expressing *Gad1*- and *Gad2*, genes that encode for enzymes responsible for GABA synthesis, also expressed *Gipr*, whereas only a few neurons expressed *Glp1r* and *Gipr* (Zhang, Kaye, et al., 2021). These data suggest the presence of two unique and very distinct neuronal circuitries within the AP and highlight the hypothesis of a local inhibitory network within the caudal hindbrain that could be exploited via activation of GIP receptors to reduce nausea and emesis mediated by hindbrain GLP-1 receptors. More exhaustive studies are required to further investigate the applications of this promising, yet understudied system.

Several GIP/GLP-1 receptor dual agonists have been or are currently being investigated in the clinical setting (see Bastin & Andreelli, 2019, for review) with none currently approved by the FDA. **Tirzepatide** (originally named LY3298176), a dual 'sequence-mixed' GIP and GLP-1 receptor agonist under development by Eli Lilly, Inc. for the treatment of T2DM, obesity and non-alcoholic steatohepatitis was designed to increase the half-life and resist enzymatic degradation to allow for once-weekly administration (Frias, 2020; Hartman et al., 2020). In addition to an Arg to Lys substitution to protect from DPP-4 degradation, its 39-amino acid structure contains a C20 unsaturated di-acid acyl side chain for enhanced albumin binding, further extending the peptide half-life to approximately 5 days (Coskun et al., 2018). Preclinical evidence showed glucose-dependent insulin secretion and improved glucose tolerance by acting on both GIP and GLP-1 receptors in mice (Coskun et al., 2018). Chronic tirzepatide treatment in a mouse model of diet-induced obesity, potently suppressed feeding, body weight and food intake with significantly greater effect than the GLP-1 receptor agonist dulaglutide (Coskun et al., 2018). Early phase trials in T2DM patients indicate that tirzepatide improves clinical outcomes beyond those achieved by a selective GLP-1 receptor agonist (Coskun et al., 2018). Phase II clinical investigations of tirzepatide actions in T2DM patients showed high efficacy for glucose handling and body weight reduction with approximately one third of patients receiving the 15-mg dose attaining normoglycaemia (defined as HbA1C < 5.7%) and one fourth of the subjects losing $\geq 15\%$ of their initial body weight after only 6 months (Frias et al., 2018). In addition, tirzepatide treatment reduced fasting glucose, insulin and triglyceride concentrations and improved insulin sensitivity. Importantly, tirzepatide showed significantly greater efficacy with regard to glucose control and weight loss than did monotherapy with a GLP-1 receptor agonist (i.e., dulaglutide), with an acceptable safety and tolerability profile (Coskun et al., 2018; Frias et al., 2018, 2020). Several large-scale Phase 3 clinical trials in T2DM (SURPASS) and obese (SURMOUNT) patients are currently

ongoing (Frias, 2020; Min & Bain, 2021), with interim positive/promising results in line with the outcome of previous studies. This general metabolic improvement further underlines the beneficial contributions of GIPR activation to GLP-1 agonist therapy.

Nausea and emesis were still present at a relatively high rate in tirzepatide-treated T2DM patients (Frias et al., 2018, 2020), despite initial Phase 1 studies suggesting a potential improved tolerance and a greater therapeutic index compared with classical GLP-1 receptor-based monotherapies (Coskun et al., 2018). The incidence of GI events was dose-related with most events being transient and categorized as mild to moderate in intensity. Nevertheless, it is surprising and contra-intuitive to the 'GIP anti-emetic hypothesis', as well as being in contrast with preclinical GIPR studies, in the context of emesis and malaise (Asami et al., 2018). Despite having an acceptable safety and tolerability profile, comparable with what is seen with GLP-1 agonist monotherapies such as dulaglutide, GI events (e.g., nausea and vomiting) were the most common adverse events related to tirzepatide treatment. One possible explanation could be that the dose range and/or the administration regime employed were suboptimal. Another possible explanation could lie in the pharmacodynamic profile of tirzepatide compared with the individual profile of the two single separate components. A recent study demonstrated that tirzepatide possesses an imbalanced agonism favouring GIP receptors over GLP-1 receptors (Willard et al., 2020). Additionally, at the GLP-1 receptor, its action is biased in favour of cAMP generation over β -arrestin recruitment, coincident with a weaker ability to drive GLP-1 receptor internalization, compared with native GLP-1 (Willard et al., 2020). Such experiments were conducted ex vivo in primary islets. Whether similar effects also occur in the CNS and whether they contribute to an enhanced 'emetic' signalling via GLP-1 receptor activation or a reduction in the GIP receptor 'anti-emetic' activity, thus cancelling the anti-emetic effects of GIP receptor signalling in the hindbrain, still need to be elucidated.

4 | GENERAL CONCLUSIONS AND OUTLOOK

After their introduction less than two decades ago, GLP-1 receptor agonists reshaped the field of diabetes care. Pharmacological side effects such as nausea and emesis have often been downplayed or dismissed, left in the shadow of the overriding goal of glucoregulation and weight loss. In recent years, differently designed strategies were employed that led, to some extent, an improved tolerability of GLP-1 receptor agonists. The data summarized here show high translational potential of new GLP-1-based approaches that will hopefully further reduce the incidence and severity of nausea and emesis, thus increasing the therapeutic efficacy, decreasing treatment attrition and extending their use to a broader population of T2DM patients (see Figure 3). In conclusion, these emerging findings demonstrate that it is possible and technically achievable to both physiologically and pharmacologically separate the emetic effects of GLP-1 receptor agonists from their glucoregulatory actions.

The use of corination combined with peptides that offer polypharmacy offers great scope for development. Combining B12 or Cbi with dual agonists of GLP-1/GIP receptors or GLP-1/NPY-Y₂ receptors is currently ongoing. In addition, the use of corination to solubilize and/or stabilize challenging peptides such as glucagon or dual agonists integrating glucagon with GLP-1 receptor agonists might solve issues with clinical development related to such problems and thus allowing the exploitation of exciting pharmacodynamic outcomes. Extensive preclinical and clinical studies investigating the effects of 'corinated' GLP-1 analogues, as well as GLP-1/GIP dual agonist(s), are required to fully evaluate the effects of these drugs in these medical conditions, and we will soon have insights into how to broaden the pharmacopoeia of GLP-1 receptor-based therapies.

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY (<http://www.guidetopharmacology.org>) and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander, Christopoulos, et al., 2019; Alexander, Fabbro et al., 2019; Alexander, Kelly, et al., 2019).

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CONFLICT OF INTEREST

T.B. and I.C.T. have no conflicts to declare. R.P.D. is an inventor of patents related to the B12/Cbi-Ex4 technology. B.C.D.J. receives research funding from Eli Lilly and Company and Pfizer Inc. and provided remunerated consultancy services for Pfizer Inc. not supporting these studies. R.P.D. is a scientific advisory board member and received funds from Xeragenx LLC (St. Louis, NY) and Balchem, New Hampton, New York, that were not used in support of these studies. M.R.H. receives research funding from Eli Lilly and Company and Boehringer Ingelheim that was not used in support of these studies.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no new data were created or analysed in this study.

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