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REVIEW

New perspectives on exploitation of incretin peptides for the treatment of diabetes and related disorders

Nigel Irwin, Peter R Flatt

Nigel Irwin, Peter R Flatt, SAAD Centre for Pharmacy and Diabetes, University of Ulster, Coleraine BT52 1SA, Northern Ireland, United Kingdom

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Correspondence to: Dr. Nigel Irwin, SAAD Centre for Pharmacy and Diabetes, University of Ulster, Cromore Road, Coleraine BT52 1SA, Northern Ireland, United Kingdom. n.irwin@ulster.ac.uk
Telephone: +44-28-70324574
Fax: +44-28-70323939

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Abstract

The applicability of stable gut hormones for the treatment of obesity-related diabetes is now undisputable. This is based predominantly on prominent and sustained glucose-lowering actions, plus evidence that these peptides can augment insulin secretion and pancreatic islet function over time. This review highlights the therapeutic potential of glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), oxyntomodulin (OXM) and cholecystokinin (CCK) for obesity-related diabetes. Stable GLP-1 mimetics have already been successfully adopted into the diabetic clinic, whereas GIP, CCK and OXM molecules offer promise as potential new classes of antidiabetic drugs. Moreover, recent studies have shown improved therapeutic effects following simultaneous modulation of multiple receptor signalling pathways by combination therapy or use of dual/triple agonist peptides. However, timing and composition of injections may be important to permit interludes of beta-cell rest. The review also addresses the possible perils of incretin based drugs for treatment of prediabetes. Finally, the unanticipated utility of stable gut peptides as effective treatments for complications of diabetes, bone disorders, cognitive impairment and cardiovascular dysfunction is considered.

Key words: Diabetes; Obesity; Incretin; Prediabetes; Gut hormones

Core tip: Stable gut hormones have well defined therapeutic actions for type 2 diabetes mellitus. In addition, simultaneous modulation of gut hormone receptors could increase therapeutic efficacy, but timing and receptor activation profile may be important. Finally, gut-derived peptides could possess benefits for bone disorders, cognitive impairment and cardiovascular dysfunction.

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INTRODUCTION

The human gastrointestinal tract (GIT) comprises the stomach, as well as the small (duodenum, jejunum

and ileum) and large (caecum, colon and rectum) intestines. Aside from nutrient digestion, absorption and assimilation, the GIT also has significant endocrine functions[1]. To date, the most important endocrine function of the gut relates to evidence that intestinal derived peptides are fundamentally involved in postprandial insulin release[2]. This action is termed the "incretin effect", and relates to the direct beta-cell insulin secretory effect of two hormones, namely glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) that are secreted from L- and K-cells, respectively (Figure 1)[3]. A number of other enteric peptide hormones released in response to feeding also have a role in energy regulation and possibly insulin secretion, including cholecystokinin (CCK) and oxyntomodulin (OXM) (Figure 1)[4,5]. However, only GLP-1 and GIP fulfil the criteria of a true incretin hormone that stimulates glucose-induced insulin secretion at physiological circulating concentrations[3]. Despite the obvious potential of incretin and incretin-like peptides for the treatment of conditions such as diabetes and obesity, the extremely short biological half-life of these peptides, due to efficient enzymatic degradation and subsequent renal filtration, severely limits therapeutic applicability[4,5]. However, interest in gut peptides has increased in recent years with knowledge that modified versions of these compounds, with vastly improved pharmacokinetic properties, have sustained beneficial physiological effects[6].

GLP-1

The biological actions of GLP-1 are largely preserved in type 2 diabetes and pharmacological doses of the peptide evoke robust insulin-releasing and antihyperglycaemic effects[7]. GLP-1 exerts its beta-cell effects through interaction with specific surface receptors that activate signal transduction pathways including the stimulation of intracellular cAMP mediated events[8]. GLP-1 also promotes beta-cell proliferation and islet cell neogenesis as well as inhibiting beta-cell apoptosis and alpha-cell glucagon secretion[8]. Notably, both GLP-1 and GIP expression and secretion has been described in islet alpha cells[9,10]. Indeed, it is feasible that intra-islet, rather than gut derived, GLP-1 and GIP make a significant contribution to these direct beneficial islet effects[11-13]. However, it should be noted that positive direct islets effects are still noted in rodents following prolonged exogenous delivery of stable GLP-1 mimetics[8].

GLP-1 not only targets pancreatic islet cells, but imparts positive actions in terms of inhibition of gastric emptying, suppression of appetite and weight loss[8]. Given this advantageous biological action profile, there are now several GLP-1 related enzyme-resistant, long-acting analogues available for clinical use in diabetes (Table 1), ranging from regimens that require twice daily injection to those that necessitate only once weekly administration[14]. Development of new GLP-1 mimetics, such as those conjugated to an antithrombin Ⅲ-binding pentasaccharide, are also in the pipeline[15]. Interestingly, a recent commentary highlights that differences in the structure and pharmacokinetics of currently available GLP-1 mimetics could significantly alter immunogenicity, CNS signalling and overall therapeutic effect[16]. Thus, physicians may need to re-evaluate the most appropriate GLP-1 treatment strategy for each patient. Encouragingly however, GLP-1-R agonists demonstrate an efficacy approaching that of insulin treatment, but unlike insulin have the added benefits of promoting weight loss with minimal risk of hypoglycaemia[17].

Despite the widespread use of GLP-1 mimetics (Table 1), there have been recent safety concerns regarding the ability of sustained GLP-1-R activation to cause pancreatitis, pancreatic and thyroid cancer, as well as glucagon-producing neuroendocrine tumours in man[18,19]. As such, it is well recognised that pancreatitis is a risk factor for pancreatic cancer[20]. However, a recent meta-analysis did not support increased risk of pancreatitis or cancer associated with GLP-1 therapy[21]. Indeed, issues with poorly matched patient groups treated with incretin-based *vs* non-incretin-based medications and problems with specifically identifying glucagon-producing cells also calls into question the validity of these safety concerns[22]. Thyroid cancer fears appear to stem largely from rodent studies[23], and reduced expression of the GLP-1 receptors in human, as opposed to rodent, thyroid cells is the likely explanation for this[24]. The most frequently reported side effect of GLP-1 therapy is dose-dependent and transient mild to moderate nausea, vomiting and diarrhoea[16]. Thus, taken together the safety profile of GLP-1 based therapeutics is largely reassuring. However, pharmacovigilance with GLP-1 drugs is still required, especially in relation to patients with a history, or increased risk, of pancreatitis or thyroid cancer.

GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE

Although initially thought to play a role in impeding histamine induced gastric acid secretion[25], the primary physiological role of GIP is now considered to be stimulation of postprandial insulin secretion[13], The insulinotropic action of GIP, mediated by specific receptors on the surface of pancreatic beta-cells, is initiated largely by intracellular cAMP generation (Figure 1) and subsequent Ca^{2+} ion influx leading to insulin granule exocytosis[13]. An additional beneficial action of GIP involves enhanced survival of beta-cells, which is also mediated through cAMP dependent cell signaling pathways[26,27]. GIP also acts as beta-cell growth factor by stimulating mitogen-activated protein kinase pathways[28] and modulating K_{ATP} channel expression[29]. Given this impressive bioactive profile at the level of the beta-cell, there has been significant interest in the potential for GIP-based pharmaceuticals as antidiabetic

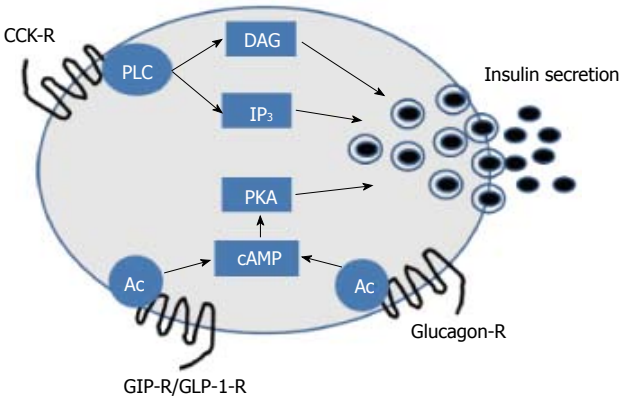

Figure 1 Schematic depicting the major signalling pathways involved in glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1, glucagon and cholecystokinin induced insulin secretion from pancreatic beta-cells. AC: Adenylyl cyclase; cAMP: Adenosine 3'-5'-cyclic monophosphate; DAG: Diacyl-glycerol; IP_3: Inositol 1,4,5-trisphosphate; PKA: Protein kinase A; PLC: Phospholipase C; CCK: Cholecystokinin.

drugs. However, like GLP-1 the pharmacokinetic profile GIP is severely hindered due to rapid plasma degradation by the ubiquitous enzyme dipeptidyl peptidase 4 (DPP-4), and clearance cleared from the body by efficient renal filtration[30]. In addition to this, the biological effects of GIP appear to be markedly reduced in patients with type 2 diabetes when compared to normal individuals[7].

The first of these barriers has been conquered, as with GLP-1 mimetics, through generation of N-terminally modified enzyme-resistant, long-acting GIP molecules, and these molecules has been reviewed extensively elsewhere[31,32]. However, the issue of reduced GIP responsiveness in type 2 diabetes still remains, and is thought to be linked to GIP receptor (GIP-R) down-regulation or desensitisation[7]. However, it is highly likely that that GIP desensitisation is a pathophysiological consequence as opposed to an aetiological factor of type 2 diabetes. In keeping with this, studies correcting hyperglycaemia using insulin or sulphonylureas indicate that GIP sensitivity can be restored[33,34]. It has also been demonstrated that a K-cell derived peptide co-secreted from the intestine with GIP, xenin-25, can potentiate the insulinotropic action of GIP[35,36]. As such, a novel long-acting palmitate-derivatised analogue of xenin-25 was shown to significantly augment GIP action *in vitro* and *in vivo*[37]. Moreover, sustained administration of this acylated xenin peptide exerted a spectrum of beneficial metabolic effects in high-fat-fed mice[38]. This presumably relates to restoration of GIP action in these diabetic mice[38]. In harmony with this, a recent study indicates that the impaired insulinotropic response to GIP under diabetic milieu involves mechanisms beyond simple expression of the GIP-R[39], further highlighting a potential role for xenin. Therefore, there still appears to be significant, as yet untapped, therapeutic potential for GIP-based compounds, especially in combination with molecules that can enhance GIP sensitivity directly or counter hyperglycaemia through other actions.

Table 1 Incretin-based drugs currently approved by the European Medicines Agency

Drug name	Primary mechanism of action	EMA approval date
Exenatide	GLP-1 receptor agonist	Nov-06
Sitagliptin	DPP-4 inhibitor	Mar-07
Vildagliptin	DPP-4 inhibitor	Sep-07
Liraglutide	GLP-1 receptor agonist	Jun-09
Saxagliptin	DPP-4 inhibitor	Oct-09
Exenatide-LAR	GLP-1 receptor agonist	Jun-11
Linagliptin	DPP-4 inhibitor	Aug-11
Lixisenatide	GLP-1 receptor agonist	Feb-13
Alogliptin	DPP-4 inhibitor	Sep-13
Dulaglutide	GLP-1 receptor agonist	Jan-15

DPP-4: Dipeptidyl peptidase 4; GLP-1: Glucagon-like peptide-1; LAR: Long-acting release; EMA: European medicines agency.

OXYNTOMODULIN

Similar to GLP-1, OXM is an L-cell derived proglucagon gene product secreted in response to feeding[40]. To date a specific OXM receptor has not been described, and the biological actions of OXM are attributed to binding and activation of GLP-1 and glucagon receptors (Figure 1), albeit with reduced potency compared to the native ligands[41]. *In vitro* and *in vivo* rodent studies suggest that through glucagon receptor agonism, OXM induces catabolic effects that favour weight loss and subsequent improved metabolic control, while glucose homeostasis and insulin resistance are improved through activation of GLP-1 receptors[5]. Promisingly, data from small clinical studies implies that beneficial effects on energy intake and weight loss also occur in humans[42,43]. However, as is this case for the incretin hormones, the therapeutic potential of OXM-based molecules is hindered by rapid cleavage of the first two N-terminal amino acids of OXM by DPP-4 in plasma, rendering the peptide inactive[44]. Nonetheless, structure-function studies show that N-terminal modification can protect against DPP-4 degradation without disproportionately affecting bioactivity of the molecule[44,45]. Indeed, a recent study of six novel OXM analogues has revealed that Oxm-based peptides with specific N-terminal position 2 modifications are stable and show particular promise for the treatment of diabetes[46]. These data suggest that further exploration of dual agonism of the GLP-1 and glucagon receptor is required for human diabetes. It is notable that co-administration of GLP-1 and glucagon in humans can replicate the beneficial actions of OXM[47], although this approach may be more cumbersome in clinical practice.

CHOLECYSTOKININ

CCK is an intestinal I-cell derived gut hormone secreted in response to meal ingestion[48]. CCK binds to specific CCK_1 receptors present on gastric mucosa and vagal afferent neurons which collectively leads to gallbladder secretions, release of pancreatic digestive juices, satiety and slowing

of gut motility[1]. CCK_2 receptors are mainly confined to the gastrointestinal tract and brain and may have a role in regulating anxiety and locomotion[49]. Importantly, CCK has also been shown to stimulate insulin secretion in rodents and man (Figure 1)[50,51], and act as a growth and anti-apoptotic factor for pancreatic beta-cells[52]. Thus, CCK agonists could have noteworthy potential for diabetes therapy, since their biological action profile is similar to the incretin hormones. However, native CCK is rapidly degraded by serum aminopeptidases upon secretion into the bloodstream[53], which hinders therapeutic potential. However, early studies have clearly shown that both N-terminal modification through glycation, or PEGylation, can prevent enzymatic degradation of CCK and extend biological action and therapeutic potential[53,54]. Following on from this, a more recently developed enzymatically stable, N-terminally modified, CCK analogue, namely (pGlu-Gln)-CCK-8, has been shown to have an improved pharmacodynamic profile, and to both alleviate and protect against obesity-related diabetes in animal models[51,55], with an encouraging safety profile[56]. The mechanism of action of (pGlu-Gln)-CCK-8 likely revolves around prominent and sustained reductions of energy intake, possibly related to modulation of central neuropeptide Y and melanocortin related pathways, and enhanced insulin release[57]. Encouragingly, a PEGylated version of (pGlu-Gln)-CCK-8 has now been fully characterised, that would be resistant to kidney filtration, and suitable for possible once daily dosing in man[58]. Further investigations relating to translation of beneficial effects to human type 2 diabetes together with safety evaluation are still required, but initial observations with specific and stable CCK_1 receptor agonists are encouraging.

MULTI-TARGET HYBRID PEPTIDE THERAPIES FOR DIABETES

Given the beneficial effects of OXM-based peptides, it follows that design of hybrid peptides capable of modulating more than one receptor pathway could have distinct therapeutic benefits for the treatment of obesity-related diabetes. By utilising the correct ratio of receptor pathway interactions, efficacy should be enhanced with the potential for administration of lower doses, thereby reducing, or removing, adverse side effects. The most logical starting point for design of a synthetic dual acting hybrid peptide would inevitably involve a modified incretin hormones capable of activating both GIP and GLP-1 receptors. As such, GIP/GLP-1 chimeric peptides were characterised almost 20 years ago, and the structural requirements for specific ligand-receptor interactions well defined[59]. Combined administration of individual long-acting GIP and GLP-1 mimetics has been considered in preclinical studies, with some success[60]. However, issues of separate drug formulation and dosing still remain, although these may not be insurmountable as indicated by recent introduction of IDegLira for combined insulin and GLP-1 therapy in type 1 diabetes[61]. In terms of a single hybrid peptide that can directly activate both GIP and GLP-1 receptors, only MAR701, Marcadia Biotech (now Roche) has progressed to the evaluation of beneficial effects in man. However, since the clinical benefits of DPP-4 inhibitors clearly involves increased circulating levels of both incretin peptides[62], concomitant activation of GIP and GLP-1 receptors does appear to have promise for the treatment of type 2 diabetes (Table 1).

Further studies have investigated the effects of GLP-1 receptor agonism combined with either glucagon receptor agonism or antagonism[63,64]. Although somewhat contradictory in nature, these contrasting regimens both utilise the beneficial glucose-lowering effects of GLP-1, combined with either inhibition of glucagon-mediated gluconeogenesis and glycogenolysis[65], or activation of glucagon pathways involved in energy turnover and weight loss[64], as is this case for OXM. Other modified hybrid peptides for dual activation of regulatory peptide receptors include, ZP3022, a combined GLP-1-gastrin agonist[66]. Through activation of GLP-1 and CCK_2 receptors, this peptide improved glycaemic control in *db/db* mice *via* enhancement of beta-cell mass[66]. However, perhaps more appealing is the potential for combined and sustained activation of GLP-1 and CCK_1 receptors. As such, two independent studies have clearly shown pronounced synergistic metabolic benefits with combined administration of long-acting GLP-1 and CCK_1 receptor agonists in rodent models of type 2 diabetes[67,68]. These extremely positive effects are believed to occur through activation of complementary pathways that lead to significant weight loss and dramatically improved metabolic control[67,68]. Furthermore, a novel CCK/GLP-1 hybrid peptide, based on the chemical structures of (pGlu-Gln)-CCK-8 and exenatide, has recently been described and shown to have significant therapeutic potential in high-fat fed mice[69]. This molecule clearly warrants further study as a potential new treatment option for type 2 diabetes.

Considering the evident therapeutic efficacy offered by dual peptide receptor interactions, single compounds with the ability to concurrently activate three or more regulatory peptide receptors could deliver even greater beneficial effects. Moreover, the celebrated success of bariatric surgery for restoring metabolic control in type 2 diabetic patients, independent of weight loss[70], results from a culmination of reduced energy intake and modulation of the secretion and biological action of numerous gut-derived peptides[71]. Thus, there is now significant enthusiasm arising from designer modified peptides with the ability to concurrently modulate GIP, GLP-1 and glucagon receptor signalling[72,73]. These triple-acting peptides have resulted in dramatic improvements in glucose homeostasis and overall metabolic control in high fat fed mice[72,73]. Despite their obvious potential, issues regarding the ratio of GIP, GLP-1 and glucagon receptor activation still need to be addressed, As such,

a subsequent study has reported the distinct beneficial effects of a balanced glucagon, GLP-1 and GIP receptor tri-agonist to correct obesity and diabetes in high fat fed mice[74]. Taken together, there is a clear and attractive rationale for further testing of combinatorial hormone therapies for the treatment of obesity and diabetes in humans.

Although the future trend for peptide-based anti-diabetic drugs seems to be development dual or triple agonists, treatment modalities that incorporate periods of beta-cell rest could be important for glycaemic control[75]. Thus, antidiabetic drugs that induce direct beta-cell stimulatory effects can erode beta-cell mass over time[76]. As such, intermittent periods of beta-cell rest may be useful to preserve long-term beta-cell function and lasting glycaemic control[75]. In contrast to sulphonylureas and meglitinides, incretin based drugs stimulate insulin secretion in a glucose-dependent fashion that should help preserve beta-cell mass and function[8]. Nonetheless, adequate periods of rest might still allow chronically stimulated pancreatic beta-cells to replenish both cell surface receptors and the immediately secretable insulin granule pool[77]. Such effects, together with the positive actions of incretins on beta-cell stimulus-secretion coupling, survival and growth, could be highly beneficial. Accordingly, the timing of injections of dual or triple acting therapies, as well as the profile of receptor pathways activated, could be of valuable clinical relevance. In relation to this, inhibition of GIP-R signalling has been shown to improve metabolic control and glycaemic status in animal models of obesity-related diabetes by enhancing insulin action and diminishing insulin secretion[78,79]. Thus a key aspect underlying the beneficial effects could be related to the induction of pancreatic beta-cell rest. Consistent with this, combination of morning injection of liraglutide, with stable GIP antagonist peptide in the evening, greatly improved glycaemic control in *db/db* mice compared with reciprocal administration or twice daily injection of liraglutide[80]. Further investigation of this potentially important treatment paradigm, in combination with other agents that stimulate and/or relieve beta cell insulin release, is required to fully explore therapeutic relevance and applicability.

INCRETIN THERAPIES AND PREDIABETES

Prediabetes describes to a situation where blood sugar is high, but not elevated sufficiently to classify as overt type 2 diabetes. However, the condition represents a high risk state for future development of diabetes, most likely linked to progressive beta-cell decline[81]. Thus, it follows that the positive effects of incretin mimetics on beta-cell function, including possible benefits for beta-cell proliferation and survival, plus additional weight-lowering and extrapancreatic actions[8], could hold significant promise for prediabetic patients. Moreover, patients with prediabetes have been shown to have an impaired incretin effect in response to oral nutrient delivery[82].

To date, there have been several tentative clinical studies conducted on the potential beneficial effects of incretin-based drugs for prediabetes. Studies with DPP-4 inhibitors (Table 1), which prevent incretin peptide degradation and increase active circulating levels of GIP and GLP-1, reported modest positive effects[83-85]. However, treatment with the stable incretin mimetics, exenatide or liraglutide, generated more positive outcomes[86,87]. This included significant reductions in the prevalence of prediabetes with reversion to normal glucose tolerance[86,87]. The inconsistency between DPP-4 inhibitors and GLP-1 mimetics most likely relates to differences in the circulating levels of active hormones achieved. However, issues of oral *vs* injectable delivery of DPP-4 inhibitors and GLP-1 mimetics, respectively, could significantly affect compliance in this patient subgroup. In addition, the potential adverse side-effect profile of incretin based therapies, as discussed above, would also have to be fully considered. Finally, the cost of therapy with DPP-4 inhibitors and particularly GLP-1 mimetics is greater when compared to other glucose-lowering agents[88]. Thus, given the limited experience to date regarding the effect of incretin therapies in prediabetes, future clinical trials would be recommended. In terms of GIP, CCK and OXM therapies, clinical effectiveness in type 2 diabetes would need to be fully established before beneficial actions in prediabetic patients could be considered.

UNEXPECTED THERAPEUTIC POTENTIAL OF INCRETIN BASED DRUGS

Bone

Although incretin hormones have been studied extensively for therapeutic effectiveness in diabetes, research has uncovered unexpected benefits in various other tissues. For instance, a role for gastrointestinal derived hormones in bone remodeling is suspected since serum levels of bone biomarkers rapidly alter after a meal[89]. Indeed, functional GIP receptors have been evidenced on the surface of bone cells[90]. Notably, GIP has been shown to inhibit bone resorption in humans under both euglycaemic and hyperglycaemic states[91]. Thus, the beneficial effects of GIP on bone could be independent of feeding state. Indeed, exogenous prolonged administration of an N-terminally modified stable GIP receptor agonist imparted various beneficial effects on tissue-level bone material properties of rats[92]. In terms of GLP-1 effects on bone, the picture is less clear. This mostly relates to data from animal models being clouded by the fact that GLP-1 receptors are highly expressed on rodent thyroid cells, resulting alterations of circulating calcitonin levels[93]. Nonetheless, GLP-1 receptors have been found on the surface of human osteoblast-like cells[94]. Moreover, very recent data suggest that liraglutide has anabolic effects on bone

in diabetic rats[95]. In keeping with this, a study in double incretin receptor knockout mice[89], reported a combination of detrimental bone abnormalities that mimicked observations from both GIP[96,97] and GLP-1[98] receptor knockout mice. Despite these observations in rodents, a preliminary meta-analysis suggests that GLP-1 mimetics do not modify the increased bone fracture risk in humans with type 2 diabetes[99], or could even potentially increase fracture risk in this population[100]. In keeping with this, a retrospective population based cohort study has suggested that DPP-4 inhibition is not associated with reduced fracture risk in humans[101], whereas bone loss and strength where significantly improved by sitaglitpin therapy in diabetic rats[102]. Care is required therefore when extrapolating data on the effects of incretin-like drugs on bone from rodents to man, particularly in the case of GLP-1. However, actions of GIP are particularly promising and further research is required to determine if incretin hormones can be useful to treat abnormalities of bone encountered in diabetes and osteoporosis.

Brain

In terms of the central nervous system, expression of functional GIP and GLP-1 receptors has been demonstrated in several brain regions[103]. Much of the therapeutic interest for incretin-like molecules in the CNS revolves around neuroprotective effects for the treatment of Alzheimer's and Parkinson's diseases, as well as cognitive impairments in diabetes[3,104]. Accordingly, GIP receptor knockout mice exhibit impaired memory learning, synaptic plasticity, and neurogenesis[105]. In agreement, transgenic mice that over-express GIP exhibit enhanced sensorimotor coordination and memory recognition[106]. Earlier studies have already shown that stable forms of GIP can beneficially modulate synaptic transmission and enhance the induction of long-term potentiation, an important physiological cellular means of monitoring learning processes[107]. In addition, prolonged GIP receptor activation improved cognitive function, hippocampal synaptic plasticity and glucose homeostasis in obese-diabetic high-fat fed mice[108]. In agreement with this, GLP-1 receptor knockout mice display an impairment of synaptic plasticity and memory formation[109]. Furthermore, sustained treatment with long-acting GLP-1 agonists improves memory and learning in various rodent models of neurodegeneration and diabetes[108,110,111]. Moreover, liraglutide treatment has recently been shown to restore cerebral and systemic microvascular architecture in a rodent model of genetically-induced cognitive dysfunction[112]. Based on the positive neuroprotective effects of incretin compounds, there are several ongoing clinical trials with these drugs that should reveal encouraging effects for the potential treatment of Alzheimer's and Parkinson's diseases[104]. Finally, in harmony with the positive effects of incretin molecules on brain function, sitaglitpin treatment was recently shown to improve recognition memory, oxidative stress and hippocampal neurogenesis in diabetic mice[113]. Collectively, these observations strengthen the possibility that incretin peptides play a direct role in modulating aspects of brain function and could possess key clinical pharmacological benefits for patients with diabetes and neurodegenerative disorders.

Heart and vasculature

The GLP-1 receptor has been demonstrated in the heart[114]. Although some controversy still exists as to the exact location of the receptor within the heart, various studies confirm the presence of GLP-1 receptor mRNA transcripts in rodent and human cardiac tissue[115]. In cardiomyocytes GLP-1 receptor signalling induced elevations in cAMP levels, but surprisingly this was not coupled to an increase in intracellular Ca^{2+} concentrations and cardiomyocyte contractility[116]. Indeed, there could be a paradoxical reduction in cardiomyocyte contractility despite elevated cAMP levels[116]. Moreover, GLP-1 receptor knockout mice present with decreased ventricular contractile function[117]. As such, the exact mechanism of action and physiological relevance of GLP-1 receptor signalling in the heart requires further detailed investigation. Despite this, and similar to the situation in pancreatic beta-cells, GLP-1 appears to have anti-apoptotic effects in cardiomyocytes and improves overall outcomes in mice after myocardial infarction[118]. Further to this, GLP-1 receptor protein has also been detected in human coronary artery endothelial cells and encouragingly, activation is believed to improve endothelial cell function in diabetic patients[119]. Thus, prospective clinical trials are ongoing to assess the cardiovascular safety profile of GLP-1 based peptides, and initial observations in humans with diabetes are positive[120]. Whilst the GIP receptor is believed to be present in the heart and on vasculature[103], there is a paucity of knowledge in relation to GIP effects on these tissues. Stimulation of GIP receptors may induce conflicting effects in different vascular beds[121], and this could explain for its unaccounted physiological effects in these tissues. In keeping with this, the overall effect of DPP-4 inhibition on cardiovascular function is still not clear[122].

FUTURE DIRECTIONS

Stable gut hormones have considerable potential for the treatment of obesity-related diabetes, and possibly other related pathologies. Whilst disorders of bone, cognitive function and the cardiovascular system can be considered as complications of diabetes, they are also standalone distinct illnesses in their own right. Thus, the therapeutic outlook of incretin mimetics may stretch well beyond diabetes. However, to date only GLP-1 based drugs are clinically available, exclusively for the treatment of type 2 diabetes and associated obesity. Concerns regarding the safety of GLP-1 analogues in man appear to have been allayed, but pharmacovigilance is still required. The potential promise of incretin based drugs

such as GLP-1 mimetics for the treatment of prediabetes still requires detailed investigation. Stable forms of GIP, OXM and CCK also appear to offer distinct therapeutic possibilities for the treatment of type 2 diabetes based on data from animal models and preliminary human studies. Given this, and the multifactorial pathological nature of diabetes, it is not unexpected that concurrent activation of more than one regulatory peptide receptor signalling pathway appears to have promise for the future treatment of diabetes. This may be achieved through the development of double or triple acting agonists or use of a cocktail of existing peptidergic drugs. However, note should be taken of emerging evidence suggesting the utility of sequential peptide exposures to facilitate essential periods of beta-cell rest. Taken together, future advances in our understanding of gut peptide biology, coupled with therapeutic application, should lead to an expansion of clinically available gut peptide-based drugs with far-reaching benefits to the patient.

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