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REVIEW

The expanding incretin universe: from basic biology to clinical translation

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Abstract

Incretin hormones, principally glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1(GLP-1), potentiate meal-stimulated insulin secretion through direct (GIP + GLP-1) and indirect (GLP-1) actions on islet β-cells. GIP and GLP-1 also regulate glucagon secretion, through direct and indirect pathways. The incretin hormone receptors (GIPR and GLP-1R) are widely distributed beyond the pancreas, principally in the brain, cardiovascular and immune systems, gut and kidney, consistent with a broad array of extrapancreatic incretin actions. Notably, the glucoregulatory and anorectic activities of GIP and GLP-1 have supported development of incretin-based therapies for the treatment of type 2 diabetes and obesity. Here we review evolving concepts of incretin action, focusing predominantly on GLP-1, from discovery, to clinical proof of concept, to therapeutic outcomes. We identify established vs uncertain mechanisms of action, highlighting biology conserved across species, while illuminating areas of active investigation and uncertainty that require additional clarification.

Keywords Alzheimer's disease · Diabetes · Heart failure · Incretin · Non-alcoholic steatosis · Obesity · Review

Abbreviations

CNS	Central nervous system
CVOT	Cardiovascular outcome trial
GIP	Glucose-dependent insulinotropic polypeptide
GIPR	Glucose-dependent insulinotropic polypeptide receptor
GLP-1	Glucagon-like peptide-1
GLP-1R	Glucagon-like peptide-1 receptor
GLP-1RA	Glucagon-like peptide-1 receptor agonist
GPR	G-protein-coupled receptor
HFpEF	Heart failure and preserved ejection fraction
IEL	Intraepithelial lymphocyte
LPS	Lipopolysaccharide
MACE	Major adverse cardiovascular events
MPGF	Major proglucagon fragment
MTC	Medullary thyroid cancer
NASH	Non-alcoholic steatohepatitis
SGLT	Sodium–glucose cotransporter
WAT	White adipose tissue

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History and discovery of incretin action

In 1902, the first hormone to regulate pancreatic exocrine secretion, secretin, was revealed [1]. It was suspected that there would also be hormonal regulation of metabolism, and after the discovery of insulin, researchers began to think about incretins, substances that could regulate insulin secretion similar to the regulation of exocrine function by excretins [2]. Since insulin could not yet be measured, these studies required complex cross-circulation experiments [3], and incretin research hardly advanced. In 1964, the radioimmunoassay for insulin enabled demonstration that oral intake of glucose resulted in greater insulin secretion than i.v. infusion (i.e. the incretin effect) [4, 5], presumably because of intestinal release of incretin hormone(s), and the hunt to identify the(se) hormone(s) began. By 1971, John Brown, who trained in the laboratory of Victor Mutt in Stockholm, had isolated a candidate hormone from porcine intestine, a peptide of 42 amino acids, which was first named as gastric inhibitory polypeptide (GIP) [6]. In 1973, Brown and John Dupré tested its possible incretin activity in humans using a purified porcine GIP preparation [7]. Indeed, GIP cause a marked potentiation of glucose-stimulated insulin secretion, and it was suggested that the peptide should be renamed

glucose-dependent insulinotropic polypeptide (allowing the acronym to be retained). Subsequent careful 'mimicry' experiments (where levels of endogenous hormone concentrations are mimicked by exogenous infusion) established GIP as an incretin hormone, which was able to virtually fully explain the incretin effect [8].

The interest in the new incretin hormone fostered hope that incretins could promote insulin secretion in people with diabetes; it was therefore disappointing when Krarup and colleagues demonstrated in 1987 that porcine GIP did not stimulate insulin secretion in people with type 2 diabetes [9], a finding that extinguished interest in the incretin concept for many. In related studies, Michael Nauck observed in 1986 that the incretin effect was lost or severely reduced in people with type 2 diabetes [10], making it unlikely that incretins would be useful therapeutically. However, it was suspected early on that incretin action was exerted by more than a single hormone. Indeed, numerous new peptides capable of stimulating insulin secretion were isolated from gut extracts in the laboratory of Erik Jorpes and Victor Mutt in Stockholm, and the wealth of new peptides inspired Werner Creutzfeldt to establish a set of criteria fulfilled by incretin hormone activity.

A candidate incretin would have to be secreted into the circulation upon glucose ingestion; neuropeptides (many of the insulinotropic peptides isolated in Mutt's laboratory and elsewhere turned out to be neuropeptides), therefore, would not qualify. It would also have to stimulate insulin secretion in relevant concentrations and at relevant plasma glucose concentrations, defined as those observed in relation to glucose intake [11]. Simultaneously, evidence was accumulating that GIP was not the only incretin, as immunoneutralisation of circulating GIP only partially reduced the incretin effect [12]. Moreover, Kjeld Lauritsen and colleagues [13] showed that the incretin effect (determined as the difference between insulin responses to isoglycaemic oral and i.v. glucose challenges) in individuals with small intestinal resections of various lengths did not correlate with GIP responses after oral glucose, but rather with the length of distal small intestine still in continuity. Thus, there had to be another incretin.

Interest focused on the products of the intestinal endocrine L cells [14], which react with antibodies towards glucagon, and glucagon was known to stimulate insulin secretion [15]. It turned out that the L cells produced a peptide of 69 amino acids, initially named glicentin, [16] which was assumed to represent at least part of 'proglucagon' [17] because it contains the full glucagon sequence at positions 33–61. Thus, glicentin (now known to be a partial form of a proglucagon precursor) (Fig. 1) was shown to be cleaved differentially in the alpha cells of the pancreatic islets (releasing glucagon) and in the L cells (releasing glicentin and a fragment corresponding to proglucagon 33–69 [designated 'oxyntomodulin']) [18]. Glicentin did not stimulate insulin secretion; oxyntomodulin did but with low potency [19] and the circulating concentrations were too low to cause stimulation of insulin secretion. At the same time, molecular biology experiments with cell-free translation of islet mRNA indicated that the real proglucagon precursor was much larger than the 69 amino acids that make up glicentin [20], engendering the question: what peptide sequences were encoded in the rest of proglucagon, designated the so called 'major proglucagon fragment' (MPGF)?

By the early 1980s, Joel Habener and colleagues deduced, based on mRNA extracted from the endocrine islet organ (Brockmann bodies) of the anglerfish, the full structure of anglerfish proglucagon and found that a glicentin-like sequence was located at the N-terminal part, but an additional glucagon-like sequence was identified in the carboxy-terminal region [21–23]. This exciting finding was followed by identification of the mammalian proglucagon sequence in 1983. Graeme Bell and colleagues identified the sequences of hamster and human proglucagon [24, 25], with other labs rapidly elucidating the bovine [26] and rat [27] proglucagon sequences. Unexpectedly, mammalian MPGF contained two glucagon-like peptide sequences (Fig. 1). However, the deduced human peptides, corresponding to proglucagon 72–107 and 126–160, were inactive with respect to insulin secretion. In contrast, native endogenous glucagon-like peptide-1 (GLP-1), extracted from human and porcine gut on the basis of reactivity with antibodies, turned out to be potently insulinotropic in a perfused pancreas preparation [28]. The endogenous intestinal GLP-1 sequence corresponded to a truncated form of GLP-1, formed by a monobasic cleavage between residues 77 and 78 in proglucagon, resulting in an amidated peptide with the full sequence of PG 78–106 amide [29]. At the same time, studies in Boston demonstrated that a similarly truncated peptide, GLP-1(7–37), stimulated glucose-dependent insulin release directly from islet cells [30] and the perfused rat pancreas [31]. A formal 'incretin analysis' in humans was published in December of 1987 from Steven Bloom's laboratory [32], clearly demonstrating the incretin-like insulinotropic potential of GLP-1, which was actually greater than that of GIP studied in the same experiments. Comparative analyses based on radioimmunoassay measurements revealed that both peptides, GLP-1 and GIP, stimulated insulin secretion at the beginning of the meal, before any appreciable increase in plasma glucose. Furthermore, their insulinotropic action was potentiated by glucose elevations corresponding to those induced by the intake of a meal [33].

Excitingly, and in contrast to GIP, GLP-1 was able to stimulate insulin secretion to virtually normal levels during a hyperglycaemic clamp in individuals with type 2 diabetes [34]. Another feature of GLP-1 was its action to inhibit glucagon secretion [35], whereas GIP stimulated glucagon secretion [36]. These properties of GLP-1 addressed both the inadequate insulin secretion and the hyperglucagonaemia characteristic of type 2 diabetes, known to underlie the pathophysiology of hyperglycaemia. Therapeutic proof of concept was provided by the observation that 4 h of GLP-1 infusion normalised blood glucose levels in people with long-standing type 2 diabetes,

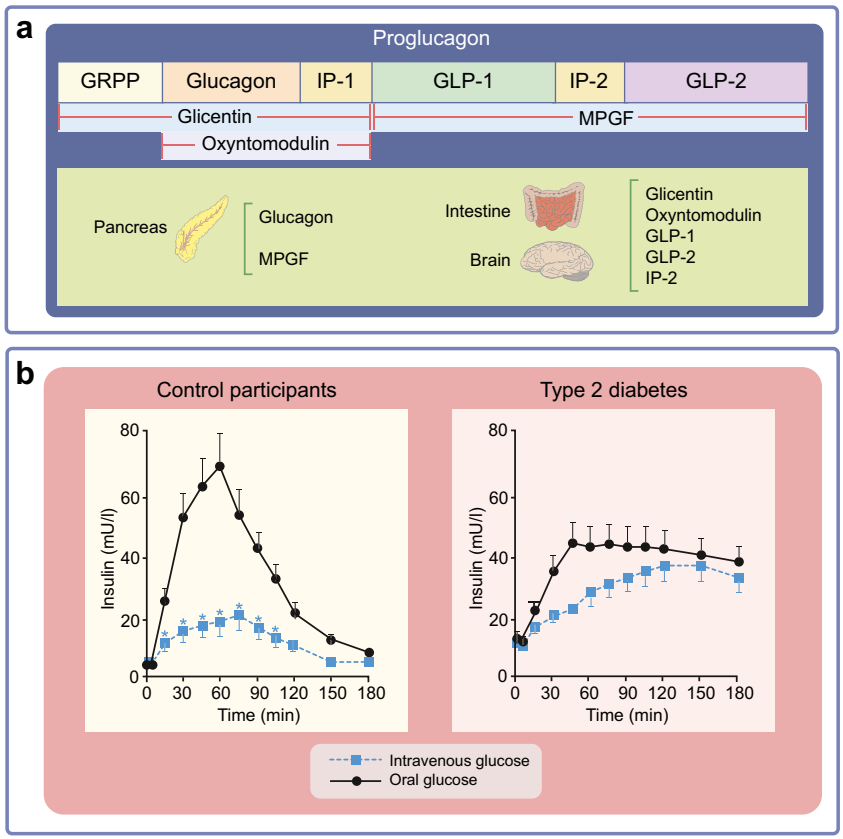

Fig. 1 (**a**) A schematic of the structure of proglucagon is shown. Processing of proglucagon-derived peptides occurs in a tissue-specific manner, with glucagon and MPGF generated in the pancreas, and glicentin, oxyntomodulin, GLP-1, GLP-2 and intervening peptide (IP)-2 generated in the intestine and brain. (**b**) The incretin effect is defined as the augmentation of insulin secretion when nutrients or glucose is administered into the gut, resulting in a greater increment in insulin secretion, relative to an isoglycaemic exposure achieved through parenteral or i.v. glucose infusion. The incretin effect is diminished in people with type 2 diabetes, largely reflecting impairment of beta cell function. Asterisks denote significant difference ($p \leq 0.05$). The original conversion factor used was 1 mU/l insulin = 7.3 pmol/l. Adapted from Nauck et al [10] with permission. This figure is available as part of a downloadable slideset

associated with increased insulin and decreased glucagon levels; importantly, these actions of GLP-1 were attenuated as glucose concentrations approached 5 mmol/l [37].

Physiology of GIP and GLP-1 in islet cells and the incretin effect

The incretin effect is of major importance for normal glucose tolerance. This was demonstrated in experiments where increasing amounts of glucose were given to volunteers either orally or (on a separate day) by i.v. infusions, yielding identical glucose excursions [38]. In these experiments, plasma glucose excursions were virtually identical despite the much larger oral vs i.v. doses, revealing a mechanism that would prevent hyperglycaemia despite the greater amounts of ingested oral glucose. The incretin effect, therefore, maintains physiologically normal glycaemic excursions, regardless of the doses of glucose or carbohydrates ingested. The underlying mechanism was revealed to be greater insulin secretion with oral vs i.v. glucose [38]. Subsequent studies showed that the secretion of the incretin hormones followed the same pattern in healthy control participants and in people with type 2 diabetes, supporting the comparatively greater stimulation of insulin secretion with ingested glucose [39].

Elucidation of the physiology of endogenous GLP-1 was enabled by use of exendin(9–39), a selective antagonist of the mammalian GLP-1 receptor [40]. Similarly, an amidated fragment of GIP, GIP(3–30)NH2, was demonstrated to be a selective and potent GIP receptor antagonist in humans [41]. Blocking both receptors by co-infusion of the incretin receptor antagonists deteriorated glucose tolerance [42], illustrating the importance of the incretin system in humans. From the measurements of insulin secretion rates, it could be calculated that GIP was responsible for about half of the insulin responses to oral glucose, while GLP-1 and glucose alone were responsible for the remaining 30% and 20%, respectively [43].

The receptors for GIP and GLP-1 are both expressed in islet beta cells, explaining their direct insulinotropic effects. GIP receptors (GIPR) and GLP-1 receptors (GLP-1R) are also expressed in subsets of alpha cells (but with GLP-1R at very low levels) [44]. Intra-islet glucagon, acting through the beta cell GLP-1R and glucagon receptors, may also contribute to the incretin effect, perhaps reconciling findings of low circulating levels of GLP-1 yet substantial meal-stimulated GLP-1R-dependent potentiation of insulin secretion [45, 46]. Similarly, incretin-like actions of GIP may also proceed indirectly through amino acids and potentiation of GIPR-dependent stimulation of glucagon secretion from alpha cells [47]. Despite structural and functional similarity of the incretin

receptors, it remains unclear why GIPR signalling is defective in type 2 diabetes; the lack of GIP responsivity has been ascribed to hyperglycaemia-associated switching of G protein signalling in beta cells [48].

Circulating levels of GIP and GLP-1 in healthy individuals and people with insulin resistance, type 2 diabetes or obesity

The majority of GLP-1-producing L cells are located in the distal gut, whereas GIP is synthesised within K cells predominantly localised to the duodenum, with a small subset of enteroendocrine cells producing both hormones [49]. GIP and GLP-1 are secreted at low levels in the fasted or interprandial state, and circulating levels rise briskly following a meal or glucose ingestion [50]. Glucose activates enteroendocrine hormone secretion via the sodium–glucose cotransporter 1 (SGLT1) [51]. Lipids and fatty acids also stimulate incretin secretion via fatty acid receptors such as G-protein-coupled receptor (GPR) 40 and GPR119 [52, 53]. The transporters and receptors coupling protein and amino acids to GIP and GLP-1 secretion are less well understood, and are mediated through diverse mechanisms, including activation of the calcium sensing receptor [54]. Oral administration of amino acids stimulates GIP as well as GLP-1 secretion in healthy humans [55].

The presence or absence of type 2 diabetes does not meaningfully impair the secretion of either hormone. In large population studies of people with type 2 diabetes, a modest impairment of GLP-1 secretion was identified [56]. Obesity, on the other hand, is frequently associated with decreased GLP-1 secretion. In animals, obesity does not impair GIP or GLP-1 secretion from isolated perfused preparations of small intestine, and weight loss does not influence GLP-1 secretion [57]. In humans with obesity, levels of GLP-1, and to a lesser extent GIP, increased after diet-induced weight loss in some [58, 59], but not all [60], studies.

GIP and GLP-1 glucoregulatory actions in type 2 diabetes

Insulin responses to both GIP and GLP-1 infused to mimic normal postprandial concentrations during a hyperglycaemic clamp were markedly diminished in people with long-standing type 2 diabetes, and were improved, but not normalised, after 4 weeks of insulin therapy [61]. Supraphysiological levels of GLP-1, but not GIP, achieved via infusion restored insulin responses to normal levels [62]. In experiments administering GIP and GLP-1 individually or together, only GLP-1 infusions lowered plasma glucose and suppressed glucagon, whereas simultaneous infusion of GIP abolished the inhibition of glucagon observed with GLP-1 [63].

Short term studies employing a 5 h infusion of GIP in individuals with type 2 diabetes who had already been treated with long-acting GLP-1R agonists (GLP-1RAs) had little acute effect on appetite or energy expenditure, and plasma glucose actually increased due to enhanced glucagon levels [64]. Similarly, continuous subcutaneous administration of native GIP for 6 days in men with type 1 diabetes increased hepatic steatosis but had little impact on a wide range of metabolic variables, including markers of bone resorption, biomarkers of inflammation, and body weight [65]. Nevertheless, unimolecular GIP–GLP-1 co-agonism is an effective therapy for type 2 diabetes, associated with weight loss and reduction of fat mass, in rats, mice, monkeys and humans [66].

A balanced GIP–GLP-1 co-agonist (equal GIP and GLP-1 potency) developed by DiMarchi and colleagues was studied in people with type 2 diabetes over 12 weeks but did not demonstrate beneficial metabolic actions beyond those achieved in an open label control arm of people treated with liraglutide [67]. In contrast, in 2018, the long-acting GIP–GLP-1 co-agonist tirzepatide was found to have substantial glucose-lowering and weight loss properties, to a greater extent than that achieved by GLP-1R agonism with dulaglutide [68], findings replicated in Phase III trials comparing tirzepatide with semaglutide in people with type 2 diabetes [69]. Tirzepatide is a biased agonist favouring cAMP production over β-arrestin recruitment, which may reduce receptor internalisation and potentially enhance GLP-1 signalling [70]

GLP-1 and control of gastric emptying: normal physiology and diabetes

GLP-1 inhibits gastrointestinal motility and gastric secretion (Fig. 2). During GLP-1 infusions, the stomach completely loses its tone and becomes flaccid [71]. In pig experiments, GLP-1 inhibited efferent vagal activity [72]. In humans, vagotomy abolished the inhibitory effects of GLP-1 on gastric emptying, as well as the inhibition of the vagal marker, pancreatic polypeptide [73]. Consistent with these findings, genetic attenuation of mouse GLP-1R expression within autonomic (including vagal) neurons reveals a role for physiological GLP-1R signalling in the basal control of gastric emptying [74]. The inhibitory effect of native GLP-1 on gastric emptying shows rapid tachyphylaxis (within hours) and disappears upon continued stimulation [75]. The inhibitory actions of long-acting GLP-1RAs on gastric emptying in people with type 2 diabetes or obesity is more variable, with substantial tachyphylaxis evident in some [76], but not all [77], studies. Reduction of gastric emptying contributes substantially to the postprandial glucose control achieved with the short acting

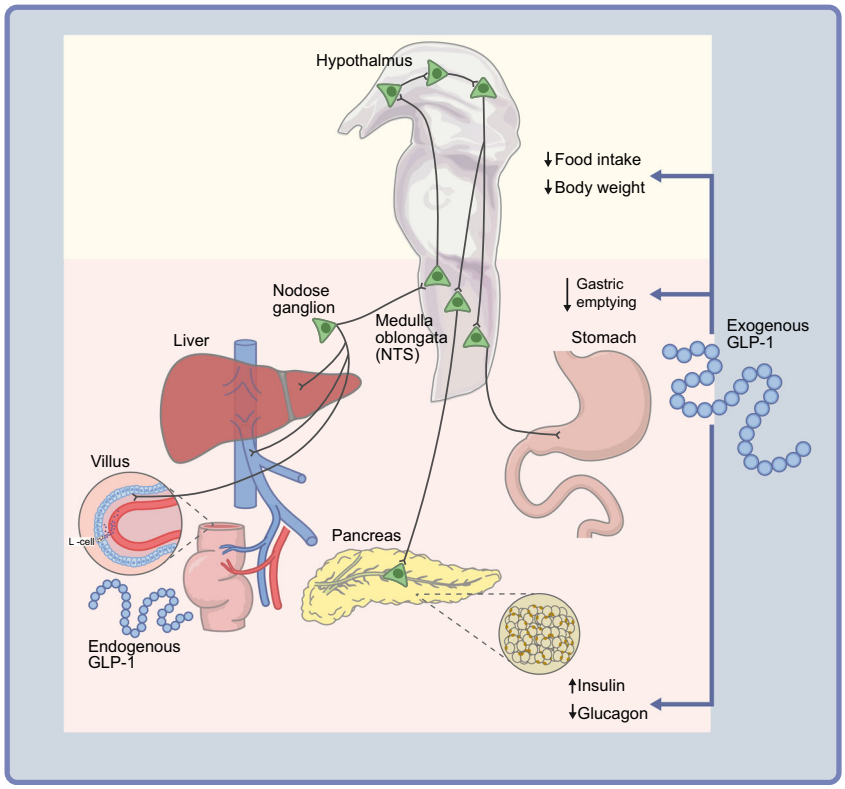

Fig. 2 Physiological vs pharmacological actions of GLP-1. Nutrients stimulate GLP-1 secretion from gut L cells, where it may engage local GLP-1R+ sensory afferent neurons within the gut originating in the nodose ganglion, which then activate neurons within the nucleus of the solitary tract (also known as the nucleus tractus solitarii; NTS). Alternatively, intrahepatic GLP-1R+ neurons, including a subset within the portal system, may be activated by circulating GLP-1and communicate ascending GLP-1R-dependent signals to the brain. Ascending fibres from solitary tract neurons may generate reflexes in the hypothalamus, and descending signals from the brainstem or hypothalamus may activate vagal motor neurons that send stimulatory or inhibitory impulses to the pancreas and the gastrointestinal tract. Exogenously administered or endogenous circulating GLP-1 may act independently of the gut–brain axis to directly engage GLP-1Rs in the brain to reduce food intake and body weight, and in the pancreas to stimulate insulin and inhibit glucagon secretion. This figure is available as part of a downloadable slideset

GLP-1RAs such as exenatide twice daily (exenatide BID) and lixisenatide. GLP-1 also attenuates small bowel motility, enhancing time for enzymatic nutrient digestion and absorption. Following gastrectomy, a higher rate of nutrient transit with energy-dense liquid meals produces a large GLP-1 secretory response, resulting in diarrhoea and, in some cases, hypoglycaemia [78]. In contrast, GIP does not impact gut motility or gastric emptying.

GIP, GLP-1 and appetite: physiology and central nervous system mechanisms

The approval of liraglutide 3 mg once daily for people with obesity was followed by the development of semaglutide 2.4 mg once weekly [79], resulting in up to 18% weight loss after 68 weeks [80]. GLP-1Rs are widely distributed in the central nervous system (CNS) (Fig. 3) [81], and the use of site-specific brain injections, together with chemogenetics targeting distinct GLP-1R+ populations, illustrates considerable redundancy in GLP-1R+ sites coupled to reduction of food intake. Although autonomic and peripheral GLP-1R+ neurons, including those within the nodose ganglion, may partially contribute to the weight loss actions of peripherally administered GLP-1RA [74, 82], ablation of CNS neurons targeted by *nestin-Cre* or *Wnt1-Cre* abolishes the anorectic actions of peripherally administered GLP-1RA in mice [74, 83]. Whether GLP-1RAs simply engage CNS GLP-1Rs accessible via circumventricular organs or are actively transported to brain regions via GLP-1Rs within the blood brain barrier, such as those expressed in tanycytes [84], remains a topic of ongoing investigation (Fig. 2).

The physiological effects of endogenous intestinal GLP-1 on food intake and body weight are comparatively modest. Although GLP-1 released from the gut may interact with local GLP-1R+ sensory nerve fibres communicating signals to the parabrachial nucleus that enable meal termination [85], the importance of these circuits for long-term control of body weight has not been established. Transient interruption of GLP-1R signalling using antagonists of the GLP-1R increases food intake and weight gain in animals [86] and humans [87]. However, GLP-1 receptor knockout mice do not become

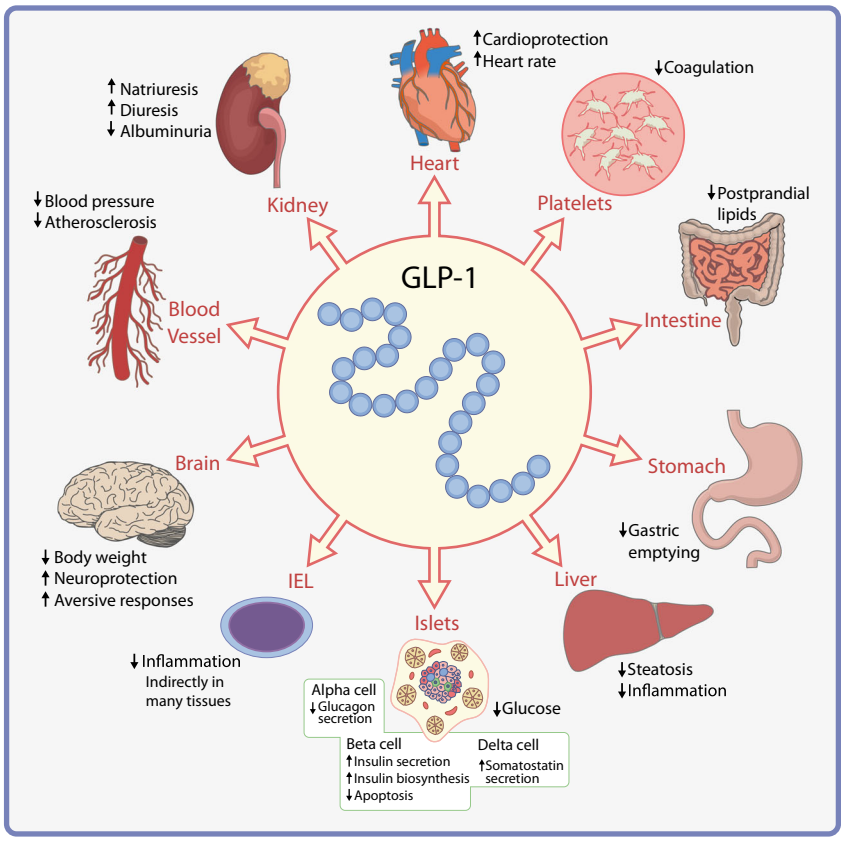

Fig. 3 The metabolic actions of GLP-1 in different organs and cell types. The actions shown are those with translational relevance predominantly conserved across species. For comparison of the actions of GIP vs GLP-1, please see review by Hammoud and Drucker [174]. Adapted from Drucker [100] with permission from Elsevier. This figure is available as part of a downloadable slideset

obese [88], and deletion of the mouse *Gcg* gene (encoding GLP-1) from the entire intestine, resulting in a 90% reduction of circulating GLP-1, does not perturb food intake or weight gain [89].

Chemogenetic activation of hypothalamic GIPR+ neurons reduces food intake in mice [90], and GIP reduces food intake when given peripherally (in mice) or via intracerebroventricular injection [91, 92]. However, its anorectic effects and impact on weight loss are comparatively modest relative to those observed with GLP-1R agonism. GIP is not known to interact with the peripheral autonomic nervous system, but its appetite inhibiting effect in rodents requires interaction with cerebral GIPR [92]. Paradoxically, reduction of intestinal GIP expression [93], GIPR antagonism [94] or genetic elimination of GIPR [95], also reduces food intake and promotes resistance to diet-induced obesity and weight loss in multiple species. GIPR agonism may indirectly potentiate the tolerability of co-administered GLP-1RA through attenuation of CNS GLP-1-activated aversive circuits [96].

GLP-1 and GIP in the cardiovascular system

GLP1 action in the cardiovascular system The widespread distribution of GLP-1R expression within the heart, blood vessels, immune system and brain regions (Fig. 3) controlling autonomic function [97–99] has sparked considerable interest in the cardiovascular biology of native GLP-1 and GLP-1RA. Both native GLP-1 and GLP-1RA exert multiple actions in the cardiovascular system, including reduction of blood pressure in hypertensive individuals, inhibition of postprandial chylomicron secretion, attenuation of inflammation in the heart and blood vessels, and reduction of ischaemic cardiac injury, but also increases in heart rate (Fig. 3) [100, 101]. Multiple long-acting GLP-1RAs reduce rates of major adverse cardiovascular events (MACE) in outcome trials of people with type 2 diabetes [102], heightening interest in understanding the mechanisms linking GLP-1R activation to cardioprotection.

Interpretation of the cardiovascular actions of native GLP-1 requires consideration that carboxy- terminal fragments, such as GLP-1(9–36) and GLP-1(28–36), the latter generated from neutral endopeptidase-mediated proteolytic cleavage, retain biological activity in the cardiovascular system through mechanisms independent of the canonical GLP-1R. These actions may be mediated through regulation of soluble adenylate cyclase 10 and mitochondrial activity controlling glycolysis and glucose oxidation [103, 104]. Nevertheless, multiple degradation-resistant and structurally distinct GLP-1RAs do not generate the same GLP-1 metabolites yet reduce blood pressure, increase heart rate, inhibit enterocyte chylomicron secretion and reduce the extent of myocardial infarction in rats and mice through mechanisms requiring the canonical GLP-1R [99, 105–108].

Delineation of mechanisms linking GLP-1R activation to cardioprotection and reduction of myocardial injury is difficult in part due to low levels of GLP-1R expression in target organs such as the heart, as well as the species-specific differences in the distribution of cardiac GLP-1Rs [98, 109]. For example, single cell RNA-seq analyses reveal that cardiac GLP-1Rs are expressed in some atrial and ventricular endothelial cells, and localised to the ventricular endocardium in mice; genetic ablation of murine GLP-1Rs within this endothelial cell population attenuates the acute cardioprotective actions of liraglutide in the setting of myocardial ischaemic injury [99]. In contrast, GLP-1Rs are relatively more abundant in human ventricles than mouse ventricles [109], and single cell RNA-seq interrogation of the normal and ischaemic human heart localises cardiac GLP-1Rs to subpopulations of atrial and ventricular cardiomyocytes [99].

GLP-1RAs also reduce the rates of stroke in cardiovascular outcome trials (CVOTs) in people with type 2 diabetes [110, 111], and are neuroprotective in experimental models of stroke and cerebral infarction (Fig. 3) [112]. Putative mechanisms linking GLP-1R activation to reduced rates of stroke are still emerging. Liraglutide attenuates thromboxane-induced platelet aggregation in people with obesity after several weeks of treatment [113], findings associated with platelet binding of LUXendin645, a fluorescent GLP-1RA, to platelets ex vivo. Moreover, the binding of LUXendin645 and the reduction of platelet aggregation by liraglutide was attenuated by the GLP-1R antagonist exendin(9–39) [113]. Nevertheless, a more careful analysis is required to determine whether human platelets express a functional canonical GLP-1R that can transduce a sustained reduction in platelet aggregation [114]. This analysis would ideally include the demonstration of full length *GLP1R* mRNA in platelets or platelet precursors.

SGLT-2 inhibitors reduce the rates of heart failure and MACE within weeks of administration [115]. However, the temporal reduction of MACE events in people with type 2 diabetes treated with GLP-1RA takes longer, becoming evident from 12 to 18 months from trial initiation [115, 116]. GLP-1RAs reduce hospitalisation for heart failure events in people with type 2 diabetes by ~11% in CVOTs [102]. However, a subset of individuals with type 2 diabetes and a history of hospitalisation for heart failure and/or impaired ventricular function (ejection fraction of <25% [117] or <35% [118]) do not exhibit improvements in heart failure and are not ideal candidates for GLP-1RA therapy. Given the association of weight loss with improved functional status in people with heart failure and preserved ejection fraction (HFpEF), the potential benefits of semaglutide are being examined in people with HFpEF (Fig. 4) and a BMI >30 with (ClinicalTrials.gov registration no. NCT04916470) or without type 2 diabetes (NCT04788511).

The time to reduction in MACE observed in the GLP-1RA CVOTs is consistent with a more chronic process, such as a reduction in atherosclerosis. GLP-1RAs reduce experimental atherosclerosis in genetically sensitised mouse models, findings associated with reduction of systemic and aortic inflammation [119, 120]. Endothelial cells are the major cellular site of GLP-1R expression in the mouse aorta; however, genetic elimination of endothelial and hematopoietic GLP-1Rs in mice with atherosclerosis did not diminish the anti-atherogenic actions of semaglutide [120]. Whether GLP-1RAs reduce vascular inflammation and atherosclerosis in people with type 2 diabetes remains uncertain. Imaging of the carotid arteries and aorta using [^{18}F]fluorodeoxyglucose positron emission tomography did not detect reduction of inflammation after 26 weeks of daily liraglutide therapy [121]. The potential benefits of semaglutide 1 mg once weekly in people with atherosclerosis and peripheral artery disease (Figs 3, 4) are being examined over 52 weeks, with the primary outcomes of treadmill walking distance and secondary outcomes of changes in quality of life and pain free walking distance (NCT04560998).

GIP action in the cardiovascular system The development of the GLP-1R–GIPR co-agonist tirzepatide for type 2 diabetes has sparked resurgent interest in the cardiovascular actions of GIP. GIPR is expressed in a subset of vascular endothelial cells, and in preclinical studies, activation of GIPR signalling attenuates, whereas loss of GIPR signalling exacerbates, the development of aortic inflammation and atherosclerosis [122, 123]. GIPRs are expressed at low levels in the mouse [124] and human heart [109] within populations of atrial and ventricular cardiomyocytes, adipocytes and pericytes [99]. Activation of GIPR signalling attenuates cardiac hypertrophy and fibrosis in mice with experimental hypertension [125], whereas loss of cardiomyocyte GIPR signalling is cardioprotective in mice with ischaemic cardiac injury secondary to coronary artery occlusion [124]. A meta-analysis of incident MACE in the Phase III tirzepatide clinical trial programme for type 2 diabetes revealed evidence for cardiovascular safety and numerically fewer MACE events in people randomised to tirzepatide therapy [126]. The cardiovascular safety of tirzepatide is also being studied in two larger dedicated CVOTs in people with type 2 diabetes, and in people living with overweight and obesity.

GLP-1 and GIP in the immune system

GLP-1-producing enteroendocrine L cells sense sterile or microbial inflammation and respond with an increase in GLP-1 secretion [101], findings reported to be mimicked by administration of cytokines [127] or lipopolysaccharide (LPS)

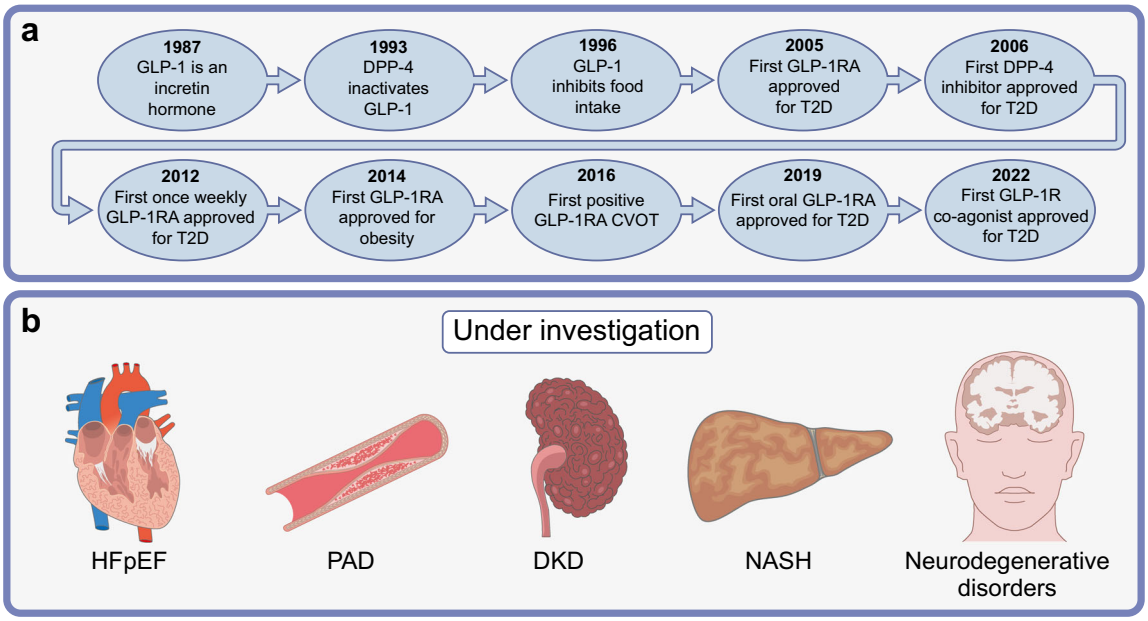

Fig. 4 Timeline of GLP-1 discovery and clinical development. (**a**) Key events in the discovery and development of GLP-1-based therapies. (**b**) Key areas of clinical investigation in late stage clinical trials. DKD, diabetic kidney disease; DPP-4, dipeptidyl peptidase-4; PAD, peripheral artery disease; T2D, type 2 diabetes. This figure is available as part of a downloadable slideset

[128]. Furthermore, blockade of the IL-6 receptor with tocilizumab reduces meal-stimulated levels of GLP-1 in people with type 2 diabetes or obesity [129]. The extent of systemic inflammation and the magnitude of increase in circulating levels of GLP-1 correlates with outcomes in people with sepsis or myocardial infarction [130, 131], although levels of GLP-1 are not universally elevated in people with acute or chronic inflammation [132]. Conversely, GLP-1RAs reduce inflammation in animals and humans with or without type 2 diabetes, independent of weight loss, with systemic anti-inflammatory actions evident within minutes to hours following acute administration of native GLP-1 [133] or GLP-1RAs [134–136].

The most abundant cellular site of GLP-1R expression in the immune system is the intestinal intraepithelial lymphocyte (IEL) (Fig. 3), and loss of *Glp1r* enhances the expression of proinflammatory biomarkers in the mouse intestine [137]. Surprisingly, despite the broad systemic anti-inflammatory actions of GLP-1RAs, much (100–1000 fold) lower levels of GLP-1R mRNA transcripts are detected in spleen, thymus, lymph nodes and hematopoietic cell lineages, relative to levels of GLP-1R expression in gut IELs [138, 139], suggesting that a substantial proportion of GLP-1 action on immune cells may be indirect. The anti-inflammatory pathways engaged by GLP-1RA to suppress T cell driven gut- and systemic inflammation, as exemplified in studies using anti-CD3, require signalling through the IEL GLP-1R [136]. In contrast, the actions of GLP-1RAs to reduce systemic inflammation, as modelled by administration of LPS, are independent of the IEL GLP-1R [136]. It seems likely that inter-organ communication, perhaps facilitated by neural pathways, contributes to the widespread anti-inflammatory actions of GLP-1 in tissues that do not contain GLP-1R+ immune cells [98].

GLP-1RAs also reduce experimental inflammation in the heart [140], islets [141], blood vessels [119], kidney [142, 143], lung [144, 145] and brain [146]. These anti-inflammatory actions may contribute to reduction of diabetes-associated complications in people treated with chronic GLP-1RA therapy. The GLP-1R is also expressed in astrocytes, and genetic loss of GLP-1Rs in mouse astrocytes increases hypothalamic inflammation and gliosis in high-fat diet-fed germ-free mice [147].

The direct and indirect anti-inflammatory actions of GLP-1RA may also contribute to resolution of hepatic inflammation in people with metabolic liver disease and non-alcoholic steatohepatitis (NASH) (Figs 3, 4) [148]. Both liraglutide and semaglutide suppress hepatic inflammation (Fig. 3) while preventing progression of fibrosis in people with NASH [149, 150]. Nevertheless, semaglutide 2.4 mg once weekly was less effective in achieving resolution of NASH when administered to individuals with both NASH and compensated cirrhosis [151]. The GLP-1R is not expressed in hepatocytes, hence the hepatic anti-inflammatory actions of GLP-1RAs are thought to be primarily indirect, perhaps secondary to weight loss [148]. The GLP-1R is expressed on a small subset of murine intrahepatic endothelial and γδ T cells, and genetic elimination of *Glp1r* in these cells attenuated the anti-inflammatory actions of semaglutide in the livers of HFD-fed mice [120]. The therapeutic potential and anti-inflammatory actions of semaglutide 2.4 mg once weekly in people with NASH (Fig. 4) is being assessed in the Phase III ESSENCE trial (NCT04822181).

GIPR is expressed at low levels in some immune cells, predominantly in subsets of T cells and macrophages [139]. Within the bone marrow, GIPR is expressed in myeloid precursors, and loss of GIPR in *Gipr*$^{-/-}$ mice, or more selective loss of the bone marrow *Gipr*, impairs formation of myeloid lineage cells [152, 153]. Conversely, administration of GIP receptor agonists to normal mice or mice exposed to chemotherapy, LPS or the TLR1/TLR2 agonist Pam3CysSerLys4 had little effect on circulating or bone marrow hematopoietic cell populations [153]. Activation of GIPR signalling reduced white adipose tissue (WAT) inflammation, characterised by reduced accumulation of monocytes and macrophages in WAT from HFD-fed mice [154]. In contrast, chronic administration of GIP to obese mice [155], or short term GIP infusion within WAT of humans [156], augments adipose tissue inflammation, characterised by increased infiltration of mononuclear cells and enhanced cytokine expression. Genetic elimination or marked reduction of GIPR in murine bone marrow or myeloid cells results in enhanced WAT and macrophage-driven inflammation, associated with upregulation of the alarmin S100A8/9 in myeloid cells [153, 157]. Although human data examining the effects of continuous GIP administration are limited, subcutaneous infusion of GIP for 6 days in men with type 1 diabetes did not alter biomarkers of inflammation in the circulation or in WAT [65].

The safety of incretin-based therapies

The widespread extrapancreatic expression of GLP-1 and GIPR raises questions surrounding the long-term consequences of incretin-based therapies for type 2 diabetes and obesity. Interpretation of reports of GLP-1R expression in some cancers is challenged by problems with accurate receptor ascertainment, reflecting use of poorly characterised antibodies with insufficient sensitivity and specificity [98, 109, 158, 159]. Interrogation of GLP-1R expression in human cancers has also been carried out indirectly using radiolabelled GLP-1R agonist and antagonist peptides. GLP-1R binding sites were detected in islet and neuroendocrine tumours, as well as in a subset of brain tumours [160]. Binding sites were also localised to a minority of ovarian and prostate cancers, although GLP-1R binding sites were not detected in colorectal, lung, liver, stomach or pancreatic cancers [160, 161]. A combination of immunohistochemistry and in situ autoradiography failed to detect GLP-1R expression in ductal pancreatic cancer or in well-differentiated thyroid cancer, although several medullary thyroid cancers contained GLP-1R+ cells [162].

The incidence of malignancy in people with type 2 diabetes treated with GLP-1RA has been scrutinised in CVOTs, as well as in real-world data. A meta-analysis of 45 trials (94,063 participants), including people with type 2 diabetes enrolled in CVOTs, did not reveal an imbalance between use of GLP-1RA and the incidence of benign or malignant thyroid disease [163]. Interrogation of real-world data sets using the Explorys system to assess cancer rates in 300 different healthcare systems in the USA following initiation of GLP-1RA therapy in 64,230 individuals with type 2 diabetes revealed lower rates of prostate, lung and colon cancer, but higher rates of thyroid cancer [164]. GLP-1RAs are contraindicated in people with a family history of medullary thyroid cancer (MTC) or multiple endocrine neoplasia type 2, and an ongoing registry of MTC cases has been established for surveillance purposes [165].

GIPR agonists have not been utilised in the clinic, hence less is known about the potential effects of manipulating GIPR signalling in the context of cancer. GIPR is upregulated in a subset of people with bilateral macronodular adrenal hyperplasia and food-induced Cushing's syndrome [166]. GIPR expression has also been detected, using in situ ligand binding, in a wide range of human neuroendocrine tumours [167]. However, the functional implications, if any, of these findings for long-term manipulation of GIPR signalling in the clinic is not known.

GLP-1, GIP and neurodegenerative disorders

Physiological and pharmacological GLP-1R signalling regulates learning, behaviour, neuronal integrity and resistance to experimental brain injury in animals [112]. Similarly, rates of stroke [110, 111], and new diagnoses and progression of cognitive impairment [168] are reduced in post hoc analyses of secondary endpoints in CVOTs of GLP-1RA in people with type 2 diabetes. Moreover, GLP-1RAs suppress neuroinflammation in preclinical studies [101, 146], and exenatide, given either twice daily or once weekly, improved disease activity scores in people with Parkinson's disease [169, 170]. Substantial preclinical data demonstrate the therapeutic potential of GLP-1RA and GIP–GLP-1RA co-agonists in mouse models of neurodegeneration, findings associated with preservation of brain structure and function, and reduction of neuroinflammation [171]. The therapeutic potential of oral semaglutide once daily is being explored in two clinical trials, in populations with and without co-existing vascular disease, studying people at risk of developing Alzheimer's disease (NCT04777396 and NCT04777409).

Summary

Substantial clinical trial and real-world data has demonstrated the efficacy and long-term safety of GLP-1RAs in people with type 2 diabetes. However, much less long-term data are available for these agents in people with obesity. Ongoing outcome trials (Fig. 4) will ascertain the risks vs benefits in people living with obesity. GLP-1RAs are also being explored in ongoing trials in people at risk for diabetic kidney disease,

people with HFpEF, people with NASH and individuals with peripheral artery disease (Fig. 4). The results of these trials will further refine, and may expand, the clinical utility of GLP-1RAs in important subpopulations with metabolic disorders. Progress in precision medicine approaches using genetics and biomarkers may identify subgroups of people that are ideally suited (or less responsive) to incretin-based therapies, enabling more targeted use of different therapeutic agents [172]. The development of tirzepatide and ongoing investigation of GLP-1-based multi-agonists has opened up an exciting new chapter in GLP-1 pharmacology [173], with an expanding range of molecules producing impressive results in early clinical trials. Each one of these agents will need to be carefully scrutinised to ensure they preserve or exceed the benefits and safety profile of GLP-1RA alone, without introduction of unanticipated new liabilities impacting therapeutic safety. Taken together, the clinical impact of GLP-1RA over 2 decades has been substantial and seems likely to be expanded, based on forthcoming clinical trial data and investigational drug development activity, in the years to come.

Supplementary Information The online version contains a slideset of the figures for download, which is available at https://doi.org/10.1007/s00125-023-05906-7.

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