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Incretin-based therapy of metabolic disease

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ABSTRACT

Incretin-based therapy of metabolic disease – a narrative review

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Recent studies show that incretin hormone analogues effectively control blood glucose while producing major weight losses and reducing the risk of all-cause mortality, myocardial infarction, stroke and kidney function impairment. Furthermore, the risk of dementia and cognitive impairment is reduced. A monomolecular coagonist (tirzepatide) of receptors for both incretin hormones (glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide) produced HbA_{1c} values below 5.7% in 50% of the treated patients and weight losses exceeding 20% in obese individuals. These new agents will radically change our approach to the treatment of T2DM and obesity alike.

KEY POINTS

- Incretin analogues (semaglutide, tirzepatide) provide effective glucose control in type 2 diabetes mellitus (T2DM) and major weight losses in people without diabetes.
- HbA_{1c} may reach normal levels in 50% of patients and weight losses by > 20% may be achieved.
- The agents reduce the risk of mortality, myocardial infarction, stroke, reduced kidney function, dementia and cognitive impairment.
- These new agents will change our therapy of T2DM and obesity.

The most recent developments regarding therapies based on incretin hormones (glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)) are likely to fundamentally change our therapy for type 2 diabetes mellitus (T2DM), obesity and conditions associated with diabetes and obesity, i. e. cardiovascular disease, stroke, cognitive impairment and diabetic kidney disease. The purpose of this review was to provide a brief account of these developments and to discuss the possible mechanisms involved.

INCRETINS

Release from the gut of incretin hormones (GIP and GLP-1) is responsible for amplification of insulin secretion,

which occurs when nutrients are taken orally rather than being infused intravenously [1]. It has been possible to map the incretin function in humans in some detail owing to the availability of receptor antagonists for both hormones, namely exendin 9-39 for the GLP-1 receptor and the amidated GIP fragment GIP 3-30 amide for the GIP receptor [2]. They both significantly influence insulin secretion and plasma glucose excursions after meals or glucose tolerance tests. The most important lesson is that if both receptors are blocked, healthy individuals will develop glucose intolerance. A quantitative analysis of insulin secretion rates based on C-peptide measurements and deconvolution showed that among the factors responsible for postprandial insulin secretion, glucose alone was responsible for 26% of the response; GLP-1 receptor activation for 29%; and GIP for the remaining 45% [2]. The picture is different in patients with T2DM in whom the incretin effect is severely impaired [3], and this undoubtedly contributes to their inappropriate insulin secretion. Evidence shows that the secretion of incretin hormones may be impaired in some patients (particularly secretion of GLP-1 in obese individuals), but the major responsible factor is a loss of beta cell responsiveness to the incretin hormones [4]. For GIP, this loss is profound and not surmountable with high doses. However, supraphysiological levels of GLP-1 (brought about by infusion) may increase glucose-stimulated insulin secretion to levels similar to those of control subjects receiving glucose alone [5]. In addition, GLP-1, but not GIP, inhibits glucagon secretion, and together these actions form the basis for the use of GLP-1 receptor agonists (GLP-1RAs) in T2DM therapy [6]. In most studies, GIP remains ineffective and may even stimulate glucagon secretion, which naturally is counterproductive. GLP-1 also inhibits gastric emptying [7], which contributes to reducing postprandial glucose excursions. This is relevant for the short-acting GLP-1 agonists, whereas tachyphylaxis rapidly develops for the long-acting agonists [8].

WEIGHT EFFECTS OF GLUCAGON-LIKE PEPTIDE-1

Exogenous GLP-1 was soon demonstrated to have other effects of interest in relation to T2DM, most importantly an inhibitory effect on appetite and food intake [9]. The inhibition, which shows dose dependency, is exerted via interactions with receptors in the brain that are accessible via leaks in the blood-brain barrier of the circumventricular organs, mainly the postrema area, the subfornical organ and the median eminence [10, 11]. Interaction with GLP-1 receptor-expressing neurons here produces further activation of important brain nuclei, including the paraventricular and the arcuate nucleus, the nucleus of the solitary tract and the nucleus ambiguous, the bed nucleus of stria terminalis, the central nucleus of the amygdala and the parabrachial nucleus [10]. Through these interactions, GLP-1 and GLP-1RAs influence appetite and food intake but also reward mechanisms, which may be very important for the clinical effects of the agonists. It has not been possible to demonstrate effects on food intake of GIP in clinical experiments.

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS IN DIABETES THERAPY; CARDIOVASCULAR RISK

These findings clearly made it attractive to exploit the GLP-1 hormone for diabetes therapy and, indeed, a continuous subcutaneous infusion of GLP-1 over six weeks produced marked reductions of glycated haemoglobin and improvements in beta cell function along with weight loss in people with advanced T2DM [12]. The sc infusion was necessary because the GLP-1 molecule is cleared extremely rapidly in the body (intravenous (IV) half-life of 1-2 min.) due to the actions of an enzyme, dipeptidyl peptidase 4 (DPP-4), which inactivates the peptide [13]. This led to the demonstration that DPP-4 inhibitors may protect the endogenous molecule [14] and to the development of clinically useful DPP-4 inhibitors, which have found clinical use worldwide. However, attempts were also made to stabilise the GLP-1 molecule against DPP-4 and also to prevent its high renal clearance rate, which in itself would result in an IV half-life of 30 min. At Novo Nordisk in Denmark, Lotte Bjerre Knudsen and colleagues utilised a technique already developed for prolongation of the action of insulin, viz.

lipidation or acylation, whereby a lipid, often a fatty acid chain, is linked to the molecule [15]. In the circulation, the fatty acid will bind to albumin, whereby the molecule acquires some of the pharmacokinetics of albumin and protects against enzymatic degradation. The analogue, liraglutide, was effective in clinical studies (the LEAD trials [16]) and was subsequently tested in a cardiovascular outcome trial, the LEADER trial [17], as demanded by the FDA for new antidiabetic agents. Although extremely costly and time-consuming, these outcome trials have, nevertheless, provided us with extremely valuable information about the natural history of the diseases, drug safety and the influence of the drugs on the disease progression. They thereby exceed considerably their original purpose, which was to document that the drugs do not increase cardiovascular risk. The trials were originally met with limited enthusiasm since several extensive outcome trials had indicated that intensified diabetes therapy was *not* associated with cardiovascular benefit; in the ACCORD trial, intensified diabetes therapy even increased mortality [18]. In agreement with expectations, the first outcome trial of a GLP-1RA, the ELIXA trial of the short-acting lixisenatide, an exendin-4 derivative with properties almost identical to those of exendin-4 or exenatide (stable, full agonists of the GLP-1 receptor), showed no increased cardiovascular risk in a patient group with severely increased CVD risk; nor did it have any beneficial effects [19]. The LEADER trial [17] was the first with a long-acting agonist (liraglutide provides a varying but relevant 24-hour exposure). Patients (n = 9,340) were randomised to liraglutide or placebo for 3.5 and up to five years and showed durable effects on glycated haemoglobin and on body weight. This was, of course, encouraging, because a concern had been raised that the beneficial effects would wane with time. Also, no signs of increased CVD risk were observed; on the contrary, the relative risk of developing major adverse cardiovascular events (MACE) was significantly reduced by about 13%.

Liraglutide was developed with a view to providing a human GLP-1 analogue with a suitable duration of action for daily use, but, inspired by its beneficial actions, the company now strived to develop a "second generation" version, optimised not only with respect to duration of action, but also with respect to effects on insulin secretion *and* food intake. The result of this effort was semaglutide. The drug had a half-life of about one week and stronger effects on glycaemia and body weight with mean reductions in HbA_{1c} of 18 mmol/mol and in body weight of 5.7 kg in the phase-III programme [20]. Indeed, in the cardiovascular outcome trial (CVOT) for semaglutide, SUSTAIN 6 – a relatively short (two-year) and small (3,297 individuals) preregistration trial (an extensive CVOT in obese individuals without T2DM (SELECT) is expected to complete in 2024) – HbA_{1c} was powerfully and durably reduced; and in this trial, the relative risk of MACE was reduced by 26% [21]. Meanwhile, several additional GLP-1RAs were developed. In a recent meta-analysis [22], it was confirmed that, as a class, the GLP-1RAs significantly reduce MACE. However, as briefly mentioned and for various reasons, data on statistical significance versus placebo were not obtained for all of the GLP-1RAs. By meta-analysis of the individual cardiovascular endpoints, significant improvements were established for all of the following: myocardial infarction, stroke, cardiovascular mortality, all-cause mortality and hospitalisation for heart failure. The effect on heart failure must be regarded as preventive rather than curative, since dedicated trials revealed no effect on any parameter associated with heart failure [23]. The effect on stroke is remarkable (and was significant in the trials of both semaglutide and dulaglutide), amounting to an 18% risk reduction, also because the other class of new antidiabetic agents with cardiovascular benefits, the SGLT2-inhibitors, show no a similar effect on stroke (but do have a significant effect on heart failure) [24]. The details and characteristics of each of the individual outcome trials were published in recent reviews [25].

In an exploratory analysis of the results of the REWIND trial, a CVOT for dulaglutide (another once-weekly GLP-1RA), a highly significant reduction of 13%-14% was observed in the risk of "substantive cognitive impairment", also after adjustment for baseline scores, age ,sex, ethnic origin or education [26]. In a pooled post-hoc analysis of data obtained with liraglutide and semaglutide, a 53% lower risk was found of dementia compared with placebo. The numbers were small but highly significant [27]. The GLP-1 agonists are also being investigated for

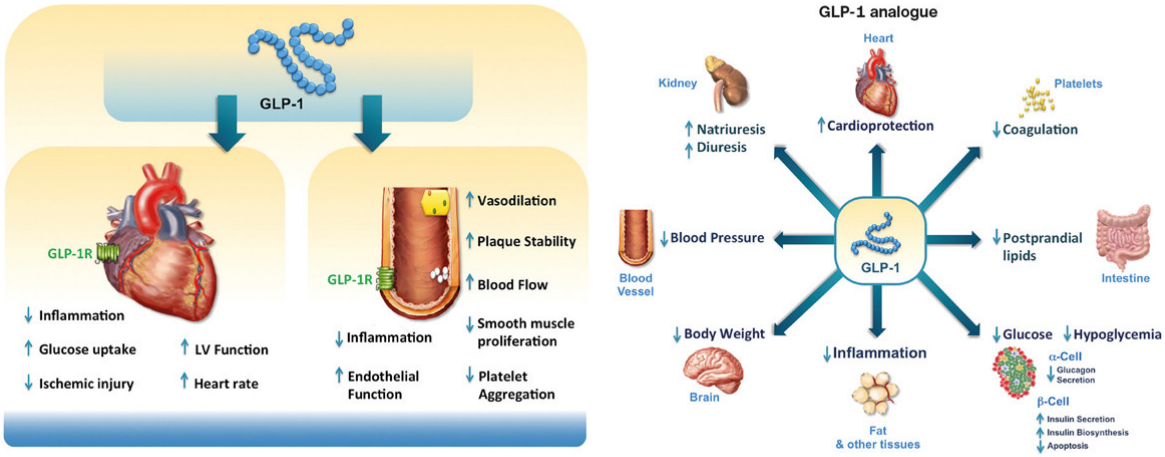
efficacy in neurodegenerative diseases including Alzheimer's and Parkinson's diseases [28].

Turning to diabetic kidney disease, beneficial effects were also found. Even the ELIXA trial showed decreasing albuminuria [19]. Moreover, a decreased risk of occurrence or worsening of a composite renal endpoint (persistent macroalbuminuria, persistent doubling of serum creatinine and creatinine clearance < 45 ml/min./1.73 m^2) was noted in the LEADER trial with liraglutide [17]; and in the SUSTAIN 6 trial, a 36% reduction was reported in the occurrence of this end point [21]. An effect on albuminuria has been observed in all of these trials [22], but whether estimated glomerular filtration rate (eGFR) was affected was less clear. However, in the AWARD 7 trial, a dedicated 52-week trial of dulaglutide in patients with diabetic kidney disease, stage 3-4, the decline with time was significantly reduced compared with insulin glargine [29]. Similarly, in a pooled analysis of results with semaglutide, a significant improvement was found in the annual impairment of eGFR, which was particularly pronounced in those with a baseline eGFR between 30 and 60 ml/min., but which remained significant in those with a higher baseline eGFR [30].

POSSIBLE MECHANISMS OF ACTION

Naturally, the outstanding question is what may be the mechanism(s) behind this remarkable spectrum of actions (**Figure 1**) [31]. Evidently, the immediate focus of treating T2DM with glucose-lowering therapy is to reduce the associated morbidity and mortality; however, as mentioned, studies aiming at intensified control have often been disappointing. Nevertheless, in a mediation analysis of the effects of liraglutide 1.8 mg in the LEADER trial [32], the CVD risk reduction was associated mainly with HbA_{1c} reductions, whereas contributions from other measured parameters (except a weak contribution from improvements in the urine albumin-to-creatinine ratio) were small. Indeed, in a systematic review with meta-analysis, Giugliano et al. [33] found a significant relationship between the reductions in HbA_{1c} and the relative risk of cardiovascular events during GLP-1RA treatment. Overweight is another important risk factor and is discussed further below. Generally, the GLP-1RAs also lower blood pressure. Still, the mechanism involved remains unexplained and surprising given that they also increase heart rate and acutely increase cardiac output. Thus, in SUSTAIN 6, a sustained, dose-related and highly significant reduction of systolic blood pressure by 5.4 mmHg relative to baseline (135 mmHg) was seen. Plasma lipids are also considered important risk factors and the GLP-1RAs appear to reduce postprandial triglycerides (again by an unknown mechanism), and apolipoprotein (Apo) B48 may be reduced in parallel, suggesting that fat absorption is reduced. On the other hand, in the SUSTAIN 6 trial, the effects on plasma lipids of the most powerful of the GLP-1RAs, semaglutide, were not remarkable; thus, only minor changes were seen in both low-density lipoprotein (LDL) and high-density lipoprotein cholesterol, free fatty acids and triglycerides [21].

FIGURE 1 Potential mode of action for glucagon-like peptide-1 to impact cardiovascular disease. Adapted from [31].



GLP-1 = glucagon-like peptide-1; GLP-1R: = glucagon-like peptide-1 receptor; LV = left ventricular.

GLP-1RAs have been proposed to have anti-inflammatory properties. Significant reductions in circulating levels of CRP have been observed in several studies, and the effect shows dose dependence [34]. However, it remains unresolved whether the anti-inflammatory effects are direct or simply reflect the weight losses. Suggestions have also been made that GLP-1RAs may directly influence and delay atherosclerosis. Thus, liraglutide attenuated lesion size in the aorta of non-diabetic ApoE -/- mice, a widely used model for accelerated atherosclerosis. The effect remained after weight matching [35]. Similarly, in LDL receptor knock-out mice subjected to a Western diet, treatment-reduced plaque lesions and semaglutide were reported to affect the expression of several genes related to cholesterol metabolism, leukocyte recruitment, adhesion and extravasation, and also extracellular matrix protein turnover [35]. A "Cardiovascular Mode of Action Trial" of semaglutide is currently being conducted (NCT04032197). It involves 100 subjects with established CVD who are treated with 1 mg semaglutide (versus placebo) for 52 weeks. It includes positron emission tomography-magnetic resonance (PET MRI) studies of plaque inflammation (plaque ^{18}F-FDG and ^{68}Ga-DOTATATE uptake), MRI for plaque morphology and burden, as well as biomarkers, proteomics and RNA profiling, myocardial perfusion reserve and changes in carotid artery total wall volume. Results are awaited by January 2023. In a recently published study of patients with T2DM, semaglutide was found to decrease the vascular uptake of ^{64}Cu-DOTATE capable of picturing activated macrophages. Furthermore, the uptake correlated with systemic levels of *high-sensitivity* C-reactive protein (CRP), supporting that semaglutide may reduce atherosclerotic inflammation by decreasing activated macrophage activity [36].

WEIGHT LOSS

It is now widely appreciated that diabetes is closely related to obesity and that major weight losses may lead to diabetes remission, whether obtained by diet or bariatric surgery. The weight loosing properties of the GLP-1RAs are therefore of major interest. The dose-related weight loosing properties of liraglutide were evident in a phase II study with increasing doses [37]. Therefore, after successful phase III studies, 3 mg liraglutide was approved for obesity therapy [38]. The second-generation GLP-1RA, semaglutide, was clearly even more effective. Thus, in a dose-response study (with daily dosing to avoid side effects), semaglutide generated weight losses of up to 14% after 52 weeks [39]. In the subsequent phase III STEP trials of semaglutide, 2.4 mg once weekly, carefully up-titrated over 20 weeks, average weight losses of up to 18% were achieved over 68 weeks in people with obesity

(start weight 107 kg) [40]. Eventually, this dose of semaglutide was approved for therapy of obesity. The cardiovascular safety of this dose of semaglutide is currently being evaluated in the SELECT trial, where 17,500 individuals with obesity and established CVD are randomised to semaglutide or placebo for 2.5-5 years. The study is estimated to complete by 28 September 2023. A dose of 2.0 mg was recently approved for diabetes therapy and showed superior HbA_{1c} and weight reductions and a similar safety profile [41].

DUAL AGONISTS OR COMBINATIONS

Semaglutide is the post powerful of the GLP-1RAs currently available, but very powerful combinations of GLP-1RAs with other weight-regulating hormones and also monomolecular agonists with dual or triple action on the receptors for these hormones are now being introduced. Most advanced is tirzepatide, a GIP-GLP-1 co-agonist, which was recently approved for diabetes therapy in the US. With this compound, weight losses of up to 22% are generated in obese individuals [42], and several of the phase III SURPASS trials of patients with T2DM have shown reductions of HbA_{1c} to values at or below 5.7% (a completely normal value) in more than 50% of the patients, accompanied by weight losses in the order of 12% [43]. In another phase II study, a fixed combination of a long-acting analogue of the islet peptide amylin ("cagrilintide") with semaglutide at 2.4 mg ("cagrisema") produced weight losses of 15.5% and 2.18% reductions in HbA_{1c} in obese individuals with T2DM [44].

CONCLUSION

The potential of these new therapies to effectively treat obesity and T2DM and radically reduce their complications pose a major challenge to the health authorities who will need to decide how these new possibilities should be implemented to the benefit of the people at risk.

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