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Editorial: Recent advances in peptide-based therapy for Type 2 diabetes and obesity

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The incidence of obesity-related Type 2 diabetes mellitus (T2DM) continues to increase worldwide at an alarming rate. This editorial attempts to highlight some recent developments in the therapeutic applications of peptides for the control of glucose homeostasis and reduction in body weight in these patients.

\textit{Glucagon-like peptide-1 receptor (GLP-1R) agonists}

The success of the naturally occurring long-acting GLP-1R agonist exendin-4 (exenatide) in lowering blood glucose concentrations in T2DM patients has led to the development of several synthetic long-acting analogs of GLP-1 that not only reduce hyperglycemia but produce weight
loss via reduced food intake and decrease the incidence of deleterious cardiovascular events in susceptible individuals. Such agents include liraglutide, lixisenatide and dulaglutide administered subcutaneously and the orally active formulation of semaglutide. These analogs contain amino acid substitutions at the Ala$^2$ residue of GLP-1 to inhibit degradation by dipeptidyl peptidase-4 (DPP-4) and attachment of an octadecanoic acid residue at Lys$^{20}$ to facilitate binding to albumin. Semaglutide was first approved as a treatment for patients with T2DM in 2017 and in 2021 also received FDA approval for chronic weight management in adults with obesity or overweight with at least one weight-related condition such as high blood pressure, T2DM, or elevated cholesterol. In a double-blind trial involving almost 2000 adults, semaglutide administered once weekly plus lifestyle intervention was associated with sustained, clinically relevant reductions in body weight [1]. A recent review concluded that in view of the beneficial metabolic and cardiovascular actions of semaglutide and the low risk for severe adverse events, the drug has an overall favorable risk/benefit profile for patients with T2DM [2]. Nevertheless, long-term use of GLP-1R agonists may involve undesirable consequences, particularly gastrointestinal side effects such as abdominal pain, nausea, vomiting and diarrhea and increased risk of cholelithiasis in some patients and may provoke immunological reactions

*Unimolecular GLP-1R co-agonists*

Studies in animal models have shown that unimolecular dual-agonist peptides that target both GLP-1R and the glucagon receptor (GCGR) and triple agonist peptides that target GLP-1R, GCGR and the glucose-dependent insulino tropic polypeptide receptor (GIPR) show some advantages compared with their constituent mono-agonist peptides in terms of their improved
actions on blood glucose control, appetite suppression, weight loss and reduction of hyperlipidemia/ hypercholesterolemia. Several long-acting hybrid peptides based upon the primary structures of GLP-1 and glucagon and upon GLP-1 and the naturally occurring GLP-1R/GCGR dual agonist, oxyntomodulin with appropriate structural modification to increase stability have been developed and have undergone Phase 1 clinical trials (reviewed in [3]). However, investigation of some compounds has been discontinued because of inferior efficacy and adverse gastrointestinal effects. It remains to be established whether therapeutic regimes involving such peptides are superior to those involving long-acting GLP-1R mono-agonists in treatment of patients with obesity-related T2DM.

Despite the fact that GIP makes a major contribution to the insulin response to nutrients in healthy subjects, the hormone was for many years neglected for therapeutic purposes because its insulinotropic activity is greatly reduced in T2DM patients. However, it has been subsequently shown that the insulinotropic potency of GIP is restored in individuals with T2DM if the hyperglycemia is first reduced by another agent. Tirzepatide is a long-acting chimeric peptide with dual agonism at both the GIP and GLP-1 receptors that, like the long-acting GLP-1R agonists, is DPP-4-resistant and contains a fatty acid albumin-binding moiety. Tirzepatide is not yet FDA approved but in a clinical trial involving once-weekly subcutaneous administration of variable doses of the agent over 40 weeks, the peptide was superior to once-weekly subcutaneous administration of the GLP-1R mono-agonist semaglutide (1 mg) in reducing HbA1c levels in patients with T2DM [4]. Reductions in body weight were also greater with tirzepatide.

*Multihormonal combination therapy*
Roux-en-Y gastric bypass (RYGB) is established as an effective treatment for patients with morbid obesity and often produces dramatic improvements in glucoregulation in such patients with T2DM. Although the precise mechanism by which the procedure ameliorates T2DM is not entirely clear, RYGB is associated with increased postprandial secretion of GLP-1, oxyntomodulin, and peptide YY. In obese patients with prediabetes/diabetes, simultaneous infusion of these peptides over a 4-week period to produce circulating concentrations mimicking those following a mixed meal resulted in improved glycemia and reduced body weight. Effects on glucose tolerance and glucose variability were superior when compared with patients who had undergone RYGB or had followed a very low calorie diet suggesting that this therapeutic regime may represent a viable alternative for treatment of obesity-related T2DM, possibly executed by development of unimolecular long-acting multi-agonist peptide [5].

Incretin peptides affecting islet cell trans-differentiation

Loss of functional β-cell mass is associated with long standing T2DM as well as with Type 1 diabetes. Progression of the disease also results in an increase in the number of α-cells and in the proportion of dedifferentiated cells that retain chromogranin-A immunoreactivity without islet hormone immunoreactivity. In addition, a subset of islet cells is converted into exocrine-like cells during disease progression. Consequently, replenishment of β-cells by proliferation of existing β-cells, protection against apoptosis, and trans-differentiation of non-β-cells into functional β-cells is an important treatment strategy. The availability of
Ins1Cre/+ ;Rosa26-eYFP and GluCreERT2 ;Rosa26-eYFP transgenic mice that enable specific labelling of α-cells in the islets with a fluorescent tag, has permitted direct α-cell lineage tracing. Administration of the DPP-4-resistant analogs [D-Ala²]GIP, or [D-Ser²,Lys³⁸]-palmitate oxyntomodulin to insulin-deficient transgenic animals for 10 days reduced apoptosis and increased proliferation of β-cells accompanied by increased trans-differentiation of glucagon positive α-cells to insulin positive β-cells [6].

Glucose-sensitive insulins

Long-acting, chemically modified analogs of insulin are effective in lowering blood glucose but can result in severe episodes of hypoglycemia. The design of glucose-sensitive insulin preparations or “smart insulins” that release the hormone in response to spikes in glucose concentrations without producing hypoglycemia has long been the aim of pharmacologists but, despite intense efforts, this goal has yet to be satisfactorily achieved. Such formulations require a glucose-binding molecular motif that will selectively respond to glucose in the relevant concentration range. Approaches include conjugation of insulin to organic macrocycles and to glucose-sensing, large molecules such as glucose oxidase, glucokinase, galactose/glucose-binding protein and the GLUT1 glucose transporter. Alternative approaches include incorporation of motifs that bind to the mannose receptor or equipping fatty acid insulin conjugates that bind to albumin with glucose-binding boronates. The concept of an insulin that is inactive at low glucose concentration but becomes active as glucose levels rise may appear to be fanciful but several attempts to synthesize such a molecule are underway. Although a
formulation suitable for use in T2DM patients has yet to be introduced, patent protections for a number of promising new compounds have recently been filed (reviewed in [7]).

Conclusion

For the foreseeable future, conventional insulin administration will no doubt remain the default intervention for T2DM patients with otherwise intractable hyperglycemia but peptide-based agents are coming increasingly to the forefront in diabetes therapy. However, none of the existing glucose-lowering agents, alone or in combination, completely normalize glycemia and prevent debilitating complications such as retinopathy, cardiovascular disease, nephropathy, neuropathy and cognitive dysfunction. This fact emphasizes the continuing need to discover safer and more effective anti-diabetic drugs.

References


