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Emerging Role Of Twincretins

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Introduction

- The prevalence of type 2 diabetes and obesity is increasing, and the need for better ways to regulate glucose homeostasis and reduce overweight in patients with diabetes is evident

- In recent years, the gut-derived incretin hormones glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1) and glucagon have attracted scientific and clinical interest for their glucose-lowering and weight reducing qualities

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Introduction

- This new class of drugs combines the beneficial effects of several independent hormones into a single entity, thereby combining their metabolic efficacy to improve systems metabolism.

- Such unimolecular drugs include single molecules with agonism at the receptors for glucagon, glucagon-like peptide 1 (GLP1) and the glucose-dependent insulinotropic polypeptide (GIP).

Introduction

- In preclinical studies, these specially tailored multiagonists outperform both their mono-agonist components and current best in class anti-obesity medications.

- While clinical trials and vigorous safety analyses are ongoing, these drugs are poised to have a transformative effect in **diabetes and anti-obesity therapy** and might hopefully lead the way to a new era in weight-loss pharmacology.

GLP-1 analogs

- GLP-1 is secreted by the intestinal L-cells in response to nutrient stimuli. GLP-1 directly acts on the β-cells to increase glucose-stimulated insulin secretion and also through the central nervous system to decrease food intake (Muller *et al.* 2017).
- These GLP-1 analogs only have modest weight-lowering efficacy, which, depending on dose and duration of treatment, typically fall in the range of 1–5 kg (Bush *et al.* 2009,
- Side effects such as nausea and GI distress preclude higher doses to drive greater weight loss.
- Therefore, it is clear that while GLP-1 analogs are beneficial to improve glycemia. Targeting solely the GLP-1 receptor for the purpose of lowering body weight has limitations.

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GLP-1/glucagon co-agonism

- The combination of GLP-1R and glucagon receptor (GCGR) agonism into a single entity seems, at first glance, counter-intuitive.

- Glucagon raises blood glucose levels by stimulating gluconeogenesis and glycogenolysis.

- However, glucagon also increases satiety after a meal and increases energy expenditure in rodents and humans (Muller *et al. 2017*).

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GLP-1/glucagon co-agonism

- The logic behind a dual agonist targeting the receptors for GLP-1 and glucagon was thus that the hypoglycemic effects of GLP-1 would buffer against any hyperglycemic liability of glucagon.

- But the anorectic effect of GLP-1 would synergize with glucagon's anorectic and thermogenic effects to ultimately drive weight loss

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GLP-1/glucagon co-agonism

- **The first patented and preclinically evaluated GLP-1/glucagon dual agonist** was developed by the groups of Richard DiMarchi and Matthias Tschöp

- **In DIO mice monitored for 7 days, a single injection of 325 nmol/kg resulted in a decrease in food intake and a body weight loss of 25%, primarily due to a loss of fat mass** (Day *et al. 2009*).

- **Weekly administration of 70 nmol/kg for 1 month resulted in a 28% decrease in body weight, primarily fat mass, as well as an improvement in glucose tolerance, and increase in the utilization of lipids as energy substrates** (Day et al. 2009).

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GLP-1/glucagon co-agonism

- A 27-day study of the same dose revealed that the co-agonist decreases:
  - plasma triglycerides, LDL cholesterol and total cholesterol, decreased circulating leptin and normalized liver lipid content (Day et al. 2009).

- These preclinical results demonstrated the multifaceted 'approach' of the co-agonist, which robustly corrects obesity and improves multiple aspects of metabolism simultaneously.

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Glucose-dependent insulinotropic polypeptide (GIP).

- GIP is a 42 amino acid protein secreted by the enteroendocrine K-cells of the proximal small intestine in response to nutrient intake (Drucker 2006).
- As an incretin hormone, the primary role of GIP is to stimulate insulin secretion .

- Recent studies demonstrate that chronic treatment with GIP can decrease body weight in rodents (Finan *et al. 2016).*

GLP-1/GIP co-agonism

- The rationale to combine the pharmacology of GLP-1 and GIP in a single entity was based on the hypothesis that such a dual incretin hormone action would maximize the glycemic benefits while the anorexigenic effect of GLP-1 would restrain any obesogenic potential of GIP

- Two unimolecular dual incretin ('twincretin') hormones were subsequently created based on the primary glucagon sequence.

- The dual-agonists incorporated key GLP-1 and GIP residues such that the peptide activated both the GLP-1R and GIPR with equal potency *in vitro* (*Finan et al. 2013*).

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GLP-1/GIP co-agonism

- Daily administration of 30 nmol/kg of the unacylated version of the dual agonist in DIO mice over the course of 7 days resulted in a 14% drop in body weight, greater than a comparable dose of exendin-4 (Finan *et al. 2013*).
- A single 30 nmol/kg dose of the 16-carbon acylated version of the peptide resulted in an 18.8% body weight drop (Finan et al. 2013).
- Both versions of the peptide decreased food intake, lowered body weight primarily through the loss of fat mass and decreased blood glucose levels (Finan et al. 2013)

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GLP-1/GIP co-agonism

- Many GLP-1R/GIPR coagonists are currently in development.
- Whether the promising preclinical results translate into clinical weight-loss benefits remains to be seen.

GLP-1/GIP/glucagon tri-agonist

- It was hypothesized that the dual insulinotropic effect of GLP-1 and GIP would optimally buffer against the diabetogenic liability of glucagon.
- While the combined agonism at the receptors for GLP-1 and glucagon would restrain any potential obesogenic effect of GIP.
- The ultimate result of such triple agonism was a profound ability to decrease body weight and to improve glycemic control.

GLP-1/GIP/glucagon tri-agonist

- In DIO mice, a 20-day study of daily subcutaneous injections of as little as 3 nmol/kg of the triple agonist resulted in a 26.6% body weight reduction, which was primarily the result of a loss of fat mass (Finan *et al. 2015a,b*).

- In addition, the triple agonist lowered blood glucose, improved glucose tolerance and lowered circulating insulin levels (Finan et al. 2015a,b), suggesting improved insulin sensitivity.

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GLP-1/GIP/glucagon tri-agonist

- The triple agonist also lowered hepatic lipid content (Finan et al. 2015a,b), which would be beneficial in a translational setting for patients with fatty liver disease and non-alcoholic steatohepatitis (NASH).

- Importantly, the metabolic benefits of the triple agonist are dependent on signaling at all three target receptors (Finan et al. 2015a,b), demonstrating that it is truly the triple agonism responsible for the observed benefits.

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Multiagonists in development

Target receptors	Drug	Company	Status
GLP-1R/GCGR	HM12525A	Hamni Pharmaceuticals	Phase II
	JNJ-54728518	Janssen Pharmaceuticals	Phase I
	MEDI0382	MedImmune	Phase II
	MK-8521	Merck	Phase II
	NN9277	Novo Nordisk	Phase I
	MOD-6030/1	Prolor/OPKO Biological	Preclinical
	SAR425899	Sanofi	Phase II
	VPD-107	Spitfire Pharma	Preclinical
	TT-401	Transition Therapeutics	Phase II/not advancing
	ZP2929	Zealand	Phase I
GLP-1R/GIPR	CPD86	Eli Lilly	Preclinical
	LY3298176	Eli Lilly	Phase II
	NN9709/MAR709/RG7697	Novo Nordisk/Marcadia	Phase II
	SAR438335	Sanofi	Phase I
	ZP-I-98	Zealand	Preclinical
	ZP-DI-70	Zealand	Preclinical
GLP-1R/GCGR/GIPR	HM15211	Hamni Pharmaceuticals	Preclinical
	MAR423	Novo Nordisk/Marcadia	Phase I

Journal of Endo[illegible]

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Twincretin: Superior glycemic control and weight loss compared to GLP-1RA monotherapy in T2DM

Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial

Aim of the study

- LY3298176 is a 39-amino acid synthetic peptide with agonist activity at both the glucose-dependent insulin-tropic polypeptide (GIP) and GLP-1 receptors, to be administered subcutaneously, once-weekly

- This randomized, double-blind, phase 2 study evaluated the dose-response relationship of LY3298176 (1, 5, 10, and 15 mg) in T2DM patients, and assessed the efficacy and safety in comparison with placebo and the GLP-1RA dulaglutide 1.5 mg.

Study design

- 316 adult patients (aged 18-75) with T2DM for at least 6 months that was
  - inadequately controlled with diet and exercise alone or
  - with stable metformin therapy for at least 3 months before screening,
  - and with a BMI of 23–50 kg/m² were randomly allocated (1:1:1:1:1:1) to one of the six parallel treatment groups for 26 weeks (placebo, LY3298176 1, 5, 10, and 15 mg, and dulaglutide 1.5 mg).

- The primary efficacy outcome was change in HbA1c from baseline to 26 weeks in the modified intention-to-treat population

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Main results

- The mean changes in HbA1c from baseline to week 26 with LY3298176 were –1.06% for 1 mg, –1.73% for 5 mg, –1.89% for 10 mg, and –1.94% for 15 mg, compared with –0.06% for placebo, and with –1.21% for dulaglutide.

- At week 26, 90% of patients treated with LY3298176 achieved the HbA1c target of less than 7.0% (vs 52% with dulaglutide and 12% with placebo), and 82% achieved the HbA1c target of at least 6.5% (vs 39% with dulaglutide and 2% with placebo)

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Main results

- Changes in fasting plasma glucose from baseline to week 26 ranged from –0.4 mmol/L (–6.8 mg/dL) to –3.4 mmol/L (–60.7 mg/dL) for the LY3298176 groups, compared with 0.9 mmol/L (15.5 mg/dL) for placebo and –1.2 mmol/L (–21.2 mg/dL) for dulaglutide.
- Largest change in fasting plasma glucose was observed with LY3298176 10 mg.
- Changes in mean bodyweight from baseline to week 26 –11.3 kg for the LY3298176 groups compared with –0.4 kg for placebo and –2.7 kg for dulaglutide.
- All doses of LY3298176 reduced bodyweight relative to placebo in a dose-dependent manner, with greater reduction in bodyweight observed with 5 mg, 10 mg, and 15 mg LY3298176 compared with dulaglutide.

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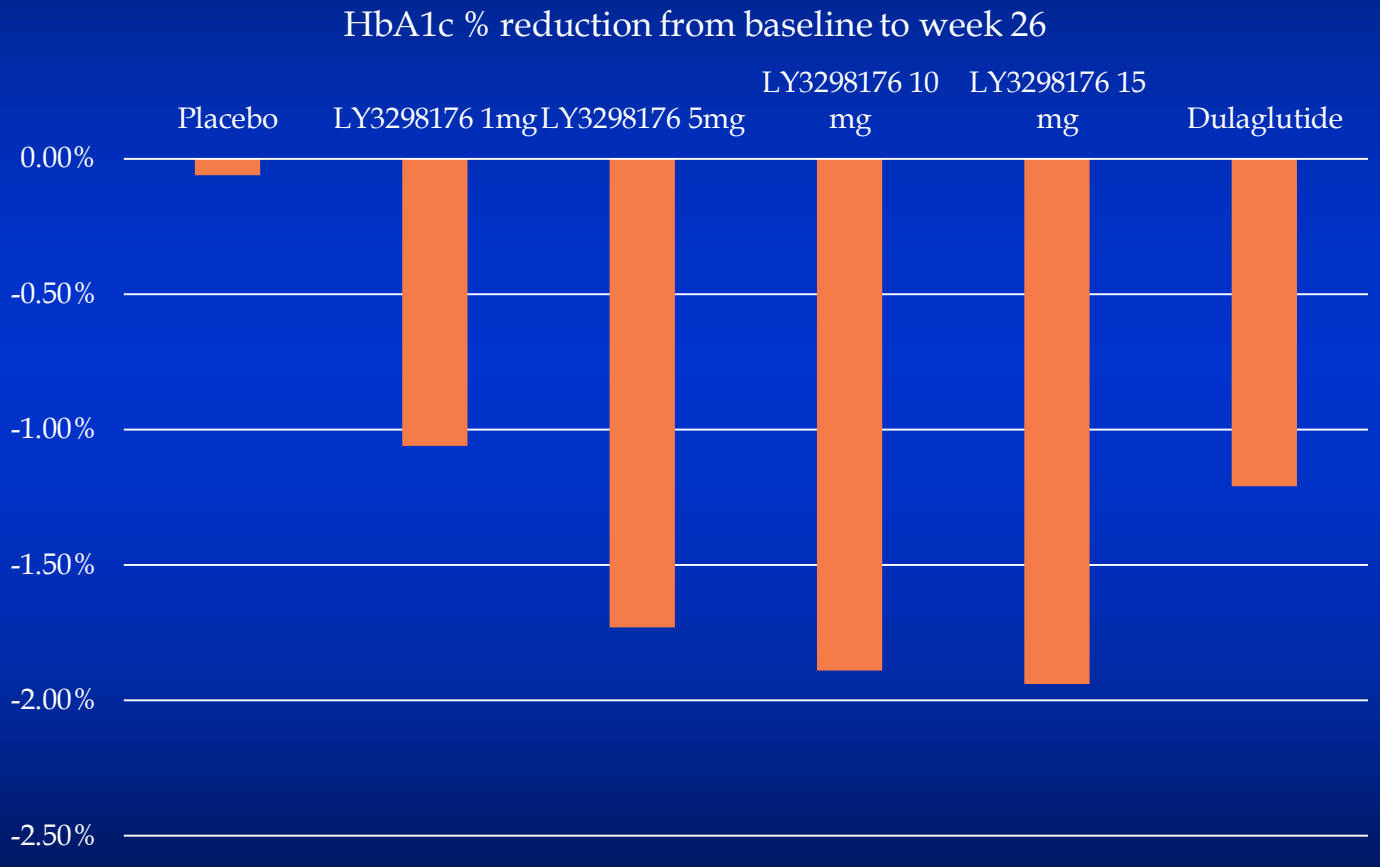
Twincretin: Superior glycemic control compared to GLP-1 RA monotherapy in T2DM

A phase 2 study (N=316; treatment duration: 26 weeks)



GIP: glucose-dependent insulin-tropic polypeptide; GLP-1: glucagon-like peptide-1; HbA1c: glycated hemoglobin

Frias et al. The Lancet 2018

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Main results

- At week 26, 14–71% of those treated with LY3298176 achieved the weight loss target of at least 5% (vs 22% with dulaglutide and 0% with placebo) and 6–39% achieved the weight loss target of at least 10% (vs 9% with dulaglutide and 0% with placebo)

- Changes in mean waist circumference from baseline to week 26 ranged from –2.1 cm to –10.2 cm for the LY3298176 groups with largest change observed after treatment with LY3298176 15 mg, compared with –1.3 cm for placebo and –2.5 cm for dulaglutide.

Main results

- In the LY3298176 groups, the number of adverse events increased in a dose-dependent manner, which was largely driven by the increasing incidence of mild or moderate gastro-intestinal adverse events (LY3298176: 23.1-66.0%, dulaglutide: 42.6% and placebo: 9.8%)

- There were no reports of severe hypoglycemia

Twincretin:

- In this phase 2b study, LY3298176, a dual GIP and GLP-1 receptor agonist, led to a statistically significant and clinically meaningful dose-dependent improvement of glucose lowering and body weight reduction compared with dulaglutide and placebo

Future .....

- With all due caution that is appropriate when analysing a study of only 26 weeks' duration, this trial is the next logical step towards replacing GLP-1 monoagonists with dual or, perhaps eventually, triple agonists.

- However, despite the small but significant competitive edge of this twincretin over a classic GLP-1 monoagonist, it is too early for any far-reaching clinical conclusion or recommendation.

- It remains to be shown in direct comparison whether an optimized twincretin will also outperform semaglutide, which is the most potent GLP-1 monoagonist to date.

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THANK YOU

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Are multiagonist peptides the golden therapy for Diabetes & obesity?

- The new class of multiagonist drugs has emerged with candidates that may finally close the gap between the efficacy seen with bariatric surgery and pharmacology

- Whereas these multiagonist peptides outperform available best in class drugs to treat obesity, only time will tell if they really represent an appreciable step forward.

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Are multiagonist peptides the golden therapy for Diabetes & obesity?

- The available preclinical data are encouraging. However, whether the efficacy and tolerability that has been demonstrated in rodents and monkeys also translates to humans remains to be seen.

- While a final judgment requires more long-term clinical studies, we can be carefully optimistic that this new class of specially engineered drugs is lighting the path to a new era in diabetes and weight-loss pharmacology.

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Are peptide conjugates the golden therapy against obesity?

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Introduction

- Diabetes and Obesity is a worldwide pandemic. Lifestyle interventions such as diet and exercise are largely ineffective and current anti-obesity medications offer little in the way of significant or sustained weight loss.
- Bariatric surgery is effective, but largely restricted to only a small subset of extremely obese patients.
- The hormonal factors mediating sustained weight loss and remission of diabetes by bariatric surgery remain elusive.
- A new class of polypharmacological drugs shows potential to shrink the gap in efficacy between a surgery and pharmacology.