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COMMENTARY

Twincretin as a potential therapeutic for the management of type 2 diabetes with obesity

Unimolecular peptide-based dual agonists against glucagon-like peptide-1 receptor (GLP-1R) and glucose-dependent insulinotropic polypeptide receptor (GIPR) have been gaining much attention recently as novel antidiabetic agents that can potentially control glycemia and bodyweight. Although GLP-1 and GIP both enhance insulin secretion and subsequently ameliorate postprandial glucose excursion, most research has focused on GLP-1R as a therapeutic target for type 2 diabetes. This is partly because the effects of GIPR activation on glycemia and bodyweight have been controversial. GIPR-deficient mice showed impaired glucose tolerance with reduced β-cell function and resistance to high-fat diet-induced obesity, whereas GIPR agonists improved glycemia and prevented high-fat diet-induced obesity in mice. Conflicting results in mice might be explained by pharmacological levels of GIP signal in the central nervous systems decreasing food intake and overcoming the obesogenic effects of GIP at physiological levels in adipose tissues. Thus, GIPR activation at pharmacological levels might result in bodyweight reduction. Indeed, bodyweight reduction by GIPR/GLP-1R dual agonists was greater than GLP-1R single agonists in individuals with type 2 diabetes. Thus, GLP-1R/GIPR dual agonists can add additional therapeutic efficacy to tailored diabetes care, especially among obese individuals with type 2 diabetes. However, caution should be exercised as to whether or not these drugs are appropriate for the management of Asian type 2 diabetes patients, which are primarily characterized by non-obesity and impaired β-cell function, as well as in that of elderly adults with type 2 diabetes, who tend to develop sarcopenia and frailty as a result of poor energy intake.

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Glucagon-like peptide-1 receptor (GLP-1R) agonists have revolutionized the management of type 2 diabetes globally. GLP-1R agonists potentiate glucose-induced insulin secretion (GIIS) from pancreatic β-cells and ameliorate glycemia with low risk of hypoglycemia; they also reduce bodyweight by activating GLP-1R in the central nervous system and suppressing appetite[1]. Accumulating evidence has confirmed the efficacy and safety of GLP-1R agonists in the management of type 2 diabetes. Furthermore, recent cardiovascular outcome studies showed that some GLP-1R agonists (i.e., liraglutide, semaglutide and dulaglutide) exert cardiovascular and renal benefits due to their effects on glycemia and bodyweight, as well as through pleiotropic effects, such as suppression of chronic inflammation and amelioration of endothelial function[1]. However, GLP-1R agonists alone or combined with available antidiabetic agents might not be sufficient to obtain appropriate control of glycemia and bodyweight in some patients with type 2 diabetes, and there is keen interest in the development of newer antidiabetic agents. Unimolecular peptide-based dual agonists against GLP-1R and the glucose-dependent insulinotropic polypeptide receptor (GIPR), as well as triple agonists against GLP-1R, GIPR and the glucagon receptor (GR), have been gaining much attention recently as novel antidiabetic agents that can potentially better control glycemia and bodyweight through simultaneous activation.

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polype ptide (GIP) are a pair of two incretin ho rmones secreted from the gut in response to ingestion of nutrients; they both enhance insulin secretion and subsequently ameliorate postprandial glucose excursion[1]. Thus, simultaneous activation of GLP-1R and GIPR might well have greater glucose-lowering abilities than their separate activation. However, most research has focused on GLP-1R as a therapeutic target for the management of type 2 diabetes; GIPR has been comparatively neglected in the past few decades. This is partly because the effects of GIPR activation on glycemia and bodyweight have been controversial[1]. Previous studies in humans showed that the insulinotropic action of GIP, unlike that of GLP-1, is blunted in individuals with type 2 diabetes with severe hyperglycemia. Importantly, recent studies showed that GIP is responsible for a substantial portion of postprandial insulin secretion in individuals with type 2 diabetes with mild hyperglycemia, suggesting that GIPR activation would be beneficial for amelioration and maintenance of glycemia in some, but not all, individuals with type 2 diabetes. It was also shown that GIPR deficiency in mice leads to impaired glucose tolerance with reduced β-cell function and resistance to high-fat diet-induced obesity[2], suggesting that GIPR activation might ameliorate glycemia, but cause bodyweight gain. In contrast, it was reported that GIP overexpression in mice results in improved glucose tolerance with enhanced β-cell function and resistance

to high-fat diet-induced obesity[3], and that chronic activation of GIPR using acylated GIP analog, (d-Ala(2))GIP[Lys(37)PAL], improves glycemia without excess bodyweight gain in high-fat diet-induced obesity in mice[4]. Importantly, the bodyweight reduction by the GIP analog was abolished by pair-feeding, suggesting that GIP agonist treatment reduces bodyweight mainly due to suppression of food intake[5]. Thus, conflicting results in GIPR-deficient mice and mice receiving GIP analog might be due to pharmacological levels of the GIP signal in the central nervous system that decrease food intake and overcome the obesogenic effects of GIP at physiological levels in the adipose tissues. However, it remains to be investigated whether GIPR activation is friend or foe in the management of type 2 diabetes in humans, especially from a bodyweight perspective (Figure 1).

Recent studies on GLP-1R/GIPR dual agonists favor beneficial effects of GIP activation in the management of type 2 diabetes. In diet-induced obese mice, a GLP-1R/GIPR dual agonist using sequence intermixed peptides resulted in more significant bodyweight reduction compared with the GLP-1R agonist, liraglutide, alone due to suppression of food intake, and ameliorated glucose and lipid metabolism. This agonist also improved and preserved β-cell mass in obese diabetic *db*/*db* mice compared with vehicle[6]. Furthermore, beneficial effects of

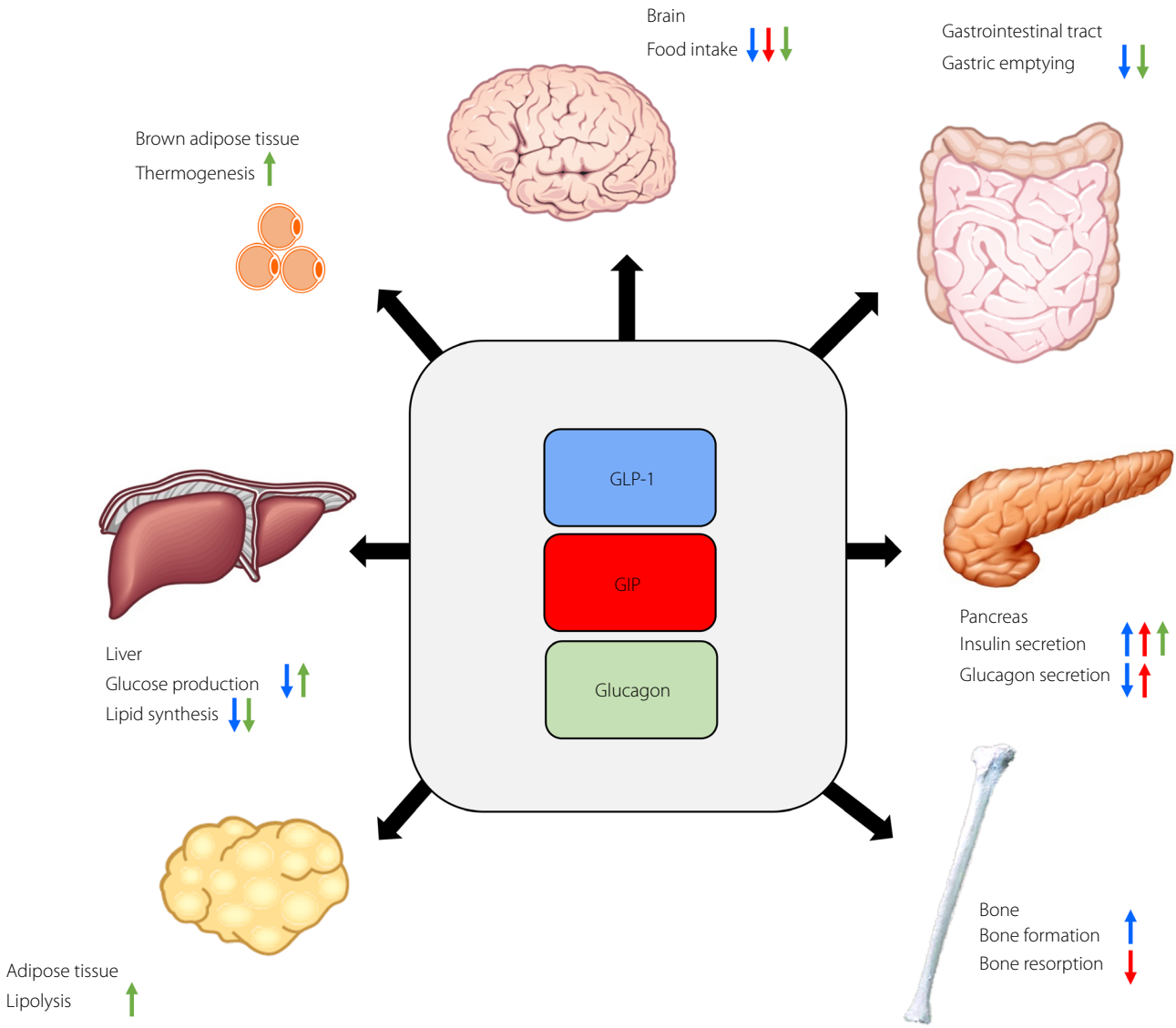

Figure 1 | Pharmacological actions of glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) and glucagon shown in humans and rodents. Blue arrows, GLP-1; red arrows, glucose-dependent insulinotropic polypeptide; green arrows, glucagon. Note that the effects of GLP-1 on bone formation were not confirmed in humans, and that the effects of GIP on glucagon secretion were observed only when glucose levels were high.

GLP-1R/GIPR agonists in the management of type 2 diabetes have been confirmed by two recently published clinical trials. The 12-week administration of 1.8 mg of the GLP-1R/GIPR dual agonist, NNC 0090-2746, developed by Novo Nordisk, significantly improved glycated hemoglobin (−0.96% vs placebo) and reduced bodyweight (−1.67% vs placebo) in patients with type 2 diabetes. Interestingly, NNC 0090-2746 reduced glycated hemoglobin similarly to 1.8 mg of liraglutide, whereas the bodyweight reduction by NNC 0090-2746 was significantly greater than that of liraglutide (−1.17% vs placebo)[7]. A 26-week treatment of GLP-1R/GIPR dual agonist, LY3298176 (Eli Lilly and Company; Indianapolis, IN, USA), also significantly reduced glycated hemoglobin in a dose-dependent manner (1 mg, −1.06%; 5 mg, −1.73%; 10 mg, −1.89%; 15 mg, −1.94%) when compared with 1.5 mg of GLP-1R dulaglutide (−1.21%) and placebo (−0.06%)[8]. Of note, the bodyweight reduction by LY3298176 (1 mg, −1.96 kg; 5 mg, −4.62 kg; 10 mg, −6.88 kg; 15 mg, −8.67 kg) was much greater than that by dulaglutide (−2.48 kg) and placebo (−0.40 kg). Although gastrointestinal adverse events with LY3298176 were more frequent (1 mg, 23.1%; 5 mg, 32.7%; 10 mg, 51.0%; 15 mg, 66.0%) than with dulaglutide (42.6%) and placebo (9.8%), GLP-1R/GIPR dual agonists (Table 1) might nevertheless be a promising drug class for the management of obese individuals with type 2 diabetes. In addition, these studies clearly showed that GIPR activation at pharmacological levels was not linked to obesity when GLP-1R was simultaneously activated.

Glucagon is released from pancreatic α-cells, and promotes hepatic glycolysis and gluconeogenesis in the liver to increase plasma glucose levels. Previous reports showed that GR-deficient mice maintain normal blood glucose levels even when the diabetic condition is introduced by streptozotocin[9], and that GR antisense oligonucleotide ameliorates hyperglycemia in *ob*/*ob* and *db*/*db* mice[10]. Thus, GR antagonists rather than GR agonists have been intensively investigated as therapeutics for type 2 diabetes in the past few decades. However, glucagon suppresses fatty acid synthesis and promotes lipolysis in adipose tissues and the liver, thereby releasing free fatty acids into the circulation as an energy source in tissues, such as skeletal muscle. Previous studies also showed that glucagon augments oxygen consumption and stimulates energy expenditure by thermogenic actions[11]. In addition, glucagon delays gastric emptying and increases satiety after a meal. Thus, GR activation might possibly be of benefit for obesity management, despite the increase in blood glucose levels. Recently, several GLP-1/GR dual agonists have been under development (Table 1). Preclinical studies showed that the GLP-1R/GR dual agonist, SAR425899 (Sanofi, Paris, France), decreased bodyweight in diet-induced obese mice and ameliorated glucose levels in *db*/*db* mice[12], and that the GLP-1R/GR dual agonist, MEDI0382 (MedImmune, Gaithersburg, MD, USA), significantly reduced bodyweight and improved glucose tolerance to levels similar to those obtained by the GLP-1R agonist, liraglutide, in non-human primates[13]. Based on the promising results with GLP-1R/GIPR and GLP-1R/GR dual agonists, GLP-1R/GIPR/GR triple agonists also have been under development as therapeutics for type 2 diabetes (Table 1). It was shown that the reduction of bodyweight by a GLP-1R/GIPR/

Table 1 | List of antidiabetic drugs targeting glucagon-like peptide-1 receptor, glucose-dependent insulinotropic polypeptide receptor and glucagon receptor

	Drug	Company	Stage
GLP-1R/GIPR	LY3298176	Eli Lilly	Phase 2
	NN9709/MAR709/RG7697	Novo Nordisk/Marcadia	Phase 2
	SAR438335	Sanofi	Phase 1
	CPD86	Eli Lilly	Pre-clinical
	ZP-I-98	Zealand	Pre-clinical
	ZP-DI-70	Zealand	Pre-clinical
GLP-1R/GR	HM12525A	Hanmi Pharmaceuticals	Phase 2
	MEDI0382	Medimmune	Phase 2
	MK-8521	Merck	Phase 2
	SAR425899	Sanofi	Phase 2
	TT-401	Transition Therapeutics	Phase 2
	JNJ-54728518	Janssen Pharmaceuticals	Phase 1
	NN9277	Novo Nordisk	Phase 1
	MOD-6030/1	Prolor/OPKO Biologics	Phase 1
	ZP2929	Zealand	Phase 1
	VPD-107	Spitfire Pharma	Pre-clinical
GLP-1R/GIPR/GR	HM15211	Hanmi Pharmaceuticals	Phase 1
	MAR423	Novo Nordisk/Marcadia	Phase 1

GLP-1, glucagon-like polypeptide-1; GR, glucagon receptor; GIP, glucose-dependent insulinotropic polypeptide.

GR triple agonist (−26.6% vs placebo) was greater than the same dose of a GLP-1/GIPR dual agonist (−15.7% vs placebo) in diet-induced obese mice[14]. Finally, these findings clearly suggest the potential benefits of GLP-1R/GIPR and GLP-1R/GR dual agonists in the management of obese individuals with type 2 diabetes, although their safety and efficacy remain to be evaluated in clinical trials.

Based the aforementioned preclinical and clinical findings, it is hoped that single polypeptides simultaneously activating GLP-1R, GIPR and GR can make additional therapeutic efficacy to tailored diabetes care, especially among obese individuals with type 2 diabetes. However, caution should be exercised as to whether or not these drugs are appropriate for the management of Asian patients with type 2 diabetes, which are primarily characterized by non-obesity and impaired β-cell function, as well as management of elderly adults with type 2 diabetes, who tend to develop sarcopenia and frailty as a result of poor energy intake.

DISCLOSURE

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