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Editorial

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GLP-1 Based Combination Therapy for Obesity and Diabetes

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INTRODUCTION

Obesity and its comorbidities, such as type 2 diabetes, are major public health diseases in modern society. Despite the currently significant unmet needs of type 2 diabetes patients, effective and safe pharmacological treatments that deliver adequate weight loss and glucose control have not been discovered.

Anorectic gut hormone, glucagon-like peptide 1 (GLP-1), is widely used to treat obesity and diabetes.[1,2] GLP-1 is a type of incretin released from the L cells of the large intestine and distal ileum when nutrients contact the intestine. In rodents and humans, GLP-1 receptor (GLP-1R) is expressed in many tissues including α, β, and δ cells of the pancreatic islets, lung, heart, kidney, stomach, intestine, pituitary, skin, nodose ganglion neurons of the vagus nerve and several regions of the central nervous system including the hypothalamus and brainstem.[3] The GLP-1 agonist, Exendin-4, has been shown to reduce food intake by slowing gastric emptying and increasing satiety.[4-9] GLP-1 exhibits an anti-diabetic effect in addition to the above-mentioned anti-obesity effect. GLP-1 potentiates glucose-stimulated insulin secretion and enhances glucose homeostasis. GLP-1 agonists usually provide significant weight reduction and glucose improvement, but only a few patients achieve adequate weight/glucose control and often experience dose-limiting adverse effects such as nausea and risk of pancreatitis.

Therefore, many researchers pursue novel therapeutics that combine GLP-1/GLP-1 agonists with other peptides such as gastric inhibitory polypeptide (GIP), glucagon and peptide YY (PYY) (Table 1). Effective combination drugs may produce synergistic effects by targeting multi-organ mechanisms (Fig. 1). In this editorial, we discuss the preclinical and clinical studies on GLP-1-based combination therapies for obesity and diabetes.

GLP-1 and GIP

GIP is a gut hormone synthesized by K cells in the mucosa of the duodenum and the jejunum of the gastrointestinal tract by binding to gastric inhibitory polypeptide receptor. Several studies have investigated the combination effects of GLP-1 and GIP on metabolic diseases. Central co-administration of GLP-1 and GIP synergistically decreased food intake and body weight.[10] Central GLP-1 and GIP co-administration significantly increased neuronal activation and pro-opiomelanocortin expression in the arcuate nucleus of the hypothalamus compared to GLP-1 or GIP alone. Peripheral co-administration of GLP-1 and GIP were investigated in several studies. When a GLP-1 or GIP analog was administered intraperitoneally to diet-induced obese

Table 1. Preclinical and clinical results of GLP-1-based combination therapies for obesity and diabetes

Combination drug	Subjects	Route	Anti-obesity			Anti-diabetes	Reference
			Food intake	Body weight	Energy expenditure	Glucose tolerance	
GIP	Mice	Central ICV	↓	↓	-	-	NamKoong et al. (2017)[10]
GLP-1/GIP co-agonist	DIO Mice	S.C.	↓	↓	-	↑	Finan et al. (2013)[11]
GLP-1/GIP co-agonist	Monkeys	S.C.	-	-	-	↑	Finan et al. (2013)[11]
GLP-1/GIP co-agonist	Lean Male Rats	S.C.	-	-	-	↑	Finan et al. (2013)[11]
GLP-1/GIP co-agonist	Healthy/ T2DM Humans	S.C.	-	-	-	↑	Finan et al. (2013)[11]
Lira-AcGIP	Swiss TO Mice	IP	-	-	-	↑	Gault et al. (2011)[12]
Lira-AcGIP	ob/ob Mice	IP	↓	↓	-	↑	Gault et al. (2011)[12]
N-AcGIP	HFD Mice	S.C.	↓	↓	-	↑	Frias et al. (2017)[13]
Glucagon	DIO Mice	S.C.	↓	↓	↑	↑	Day et al. (2009)[14]
Glucagon	Obese Humans	IV	↓	-	↑	-	Cegla et al. (2014)[15]
Glucagon	Obese Humans	IV	-	-	↑	-	Tan et al. (2013)[16]
GLP1/GIP/Glucagon triagonist	DIO Mice	S.C.	↓	↓	↑	↑	Finan et al. (2015)[17]
GLP1/GIP/Glucagon triagonist	HFD Mice	IP	↔	↓	-	↑	Gault et al. (2013)[18]
PYY	Healthy Humans	IV	↓	-	-	-	De Silva et al. (2011)[23]
PYY 3-36	Healthy Humans	PO	↓	-	-	-	Steinert et al. (2010)[24]
PYY 3-36	Mice	IP	↓	↔	-	-	Talsania et al. (2005)[25]
CCK-33	Healthy Humans	IV	↓	-	-	-	Gutzwiller et al. (2004)[26]
Leptin	Rats	IP	↓	-	-	-	Akieda-Asai et al. (2014)[27]
Leptin	Rats	IP	↓	↓	-	-	Bojanowska et al. (2007)[28]
Naltrexone (Opioid antagonist)	Rats	IP	↓	-	-	-	Liang et al. (2013)[29]
Salmon Calcitonin (Amylin analog)	Monkeys	Intramuscular	↓	-	-	-	Bello et al. (2010)[30]
Gastrin	db/db Mice	IP	-	-	-	-	Tamaki et al. (2010)[32]
Gastrin	Mice	IP	-	-	-	-	Suarez-Pinzon et al. (2008)[33]

GLP-1, glucagon-like peptide 1; GIP, gastric inhibitory polypeptide; ICV, intracerebral ventricular; DIO, diet-induced obesity; S.C., subcutaneous; T2DM, type 2 diabetes; AcGIP, acylated gastric inhibitory polypeptide; TO, tuck ordinary; IP, intraperitoneal injection; HFD, high fat diet; PYY, peptide YY; IV, intravenous; PO, per os; CCK, cholecystokinin.

(DIO) mice, the GLP-1 analog decreased body weight (15.4%).[11] A comparable dose of the GIP analog did not cause significant metabolic improvements. However, co-administration of GLP-1 and GIP decreased fat mass and body weight (20.8%) and reduced food intake more than GLP-1 or GIP alone. Based on the enhanced efficacy of GLP-1 and GIP co-administration, a single-molecule GLP-1/GIP co-agonist was investigated. This acylated co-agonist or liraglutide (an acylated GLP-1 analog) was administered to DIO mice for 4 weeks. The treatment with unimolecular co-agonist resulted in greater metabolic improvements than a

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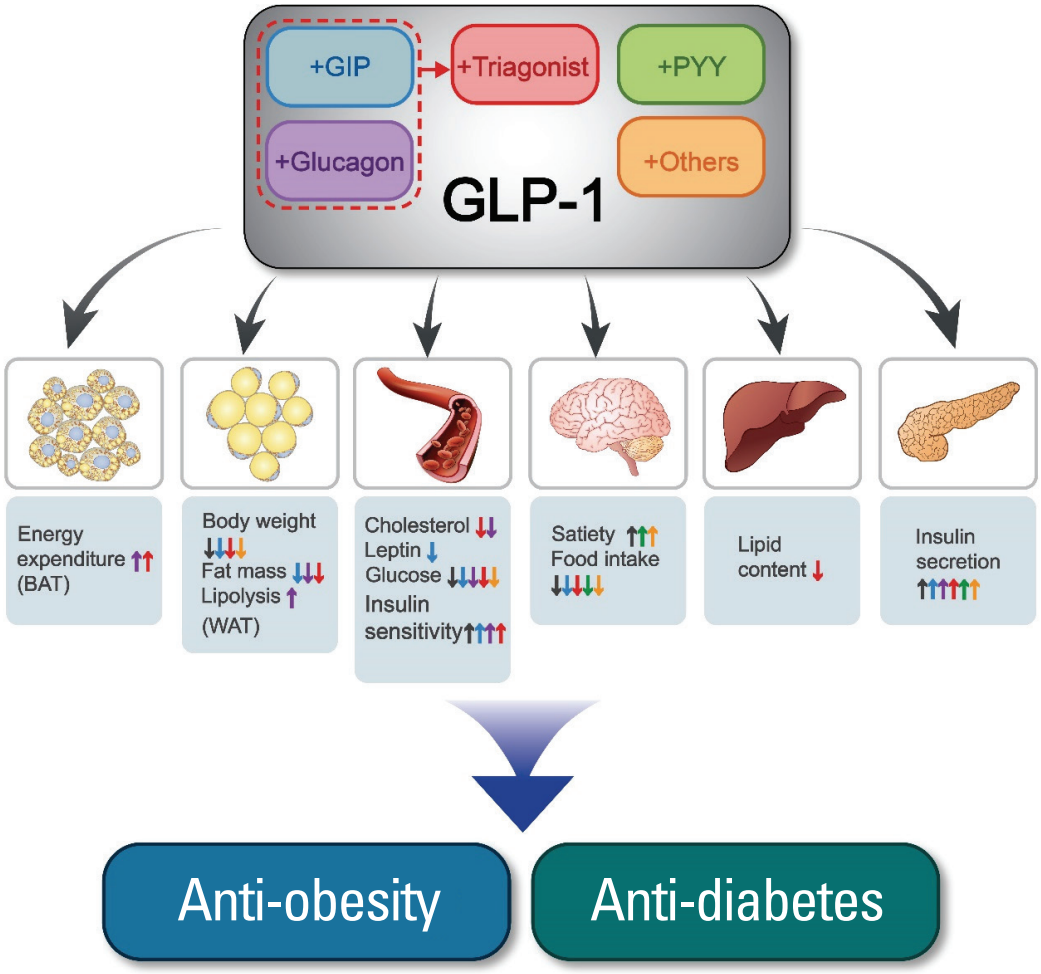

Figure 1. Metabolic actions of GLP-1-based combination therapy on major organs (BAT, WAT, circulation, brain, liver and pancreas). GIP, gastric inhibitory polypeptide; PYY, peptide YY; GLP-1, glucagon-like peptide 1; BAT, brown adipose tissue; WAT, white adipose tissue.

similar dose of liraglutide. The enhanced insulinotropic effect of unimolecular dual incretins was also observed in nonhuman primates. Enhanced insulin secretory response in cynomolgus monkeys increased plasma insulin and C-peptide. In human studies, unimolecular dual incretin treatment caused rapid and significant decrease in HbA1c (hemoglobin A1c) without vomiting and minimal adverse effects. In another study, acylated analogs of GLP-1 and GIP were shown to affect weight loss, modify plasma glucose level and significantly modify insulin responses in mice with diabetes.[12] In a recent study, dual unimolecular incretins (fatty-acylated GLP-1/GIP receptor agonist) significantly reduced HbA1c, cholesterol, leptin and body weight in patients with type 2 diabetes.[13] Based on mouse, non-human primate and human studies, the combination of GLP-1 and GIP showed promising potential for anti-obesity and anti-diabetic therapies.

GLP-1 and glucagon

Glucagon and GLP-1 are the first products produced when proglucagon is processed in the pancreas and gut, respectively. Glucagon is secreted by α cells of the pancreas, binds to receptors mainly expressed on liver and kidney and increases blood glucose levels by activating hepatic glucose production. Preclinical studies in DIO mice showed the administration of glucagon/GLP-1 co-agonist normalized adiposity by activating white adipose tissue (WAT) lipolysis and increased insulin sensitivity and glucose tolerance.[14] Acute co-infusion of low doses of GLP-1 and native glucagon increased energy expenditure synergistically.[15] Experiments performed in humans indicated the combination of gluca-

gon and GLP-1 synergistically increases resting energy expenditure and insulin level.[16] In both preclinical and clinical studies, the combination of GLP-1 and glucagon showed anti-diabetic and anti-obesity synergistic effects.

Unimolecular GLP-1/GIP/glucagon triagonist

Due to recently developed high-technology approaches, research focusing on unimolecular co-agonists is currently being conducted. In particular, the 3 hormones, GLP-1, GIP and glucagon, have unique enteroinsular effects as well as roles in the regulation of energy and glucose homeostasis. Several studies reported the unimolecular, balanced, GLP-1/GIP/glucagon triagonist is superior to the respective dual agonists.[17,18] At a low dose, liraglutide and the GIP/glucagon co-agonist did not improve body weight, whereas triagonist decreased body weight by 15.1%.[17] The co-agonist and the triagonist were both equally effective in improving glucose tolerance and decreasing ad libitum–fed blood glucose without hypoglycemia. However, the triagonist decreased the plasma concentrations of insulin more than the co-agonists, indicating insulin sensitivity improved more with a triagonist than with a co-agonist. Furthermore, the triagonist lowered the circulating concentration of cholesterol thus lowering hepatic lipid content and hepatocellular vacuolation. Enhanced energy expenditure was also observed in triagonist-treated DIO mice compared with pair-fed controls. In another study, GLP-1/GIP/glucagon triagonist decreased body weight, exerted insulin secretory actions and improved both glucose tolerance and insulin resistance in mice fed a high-fat diet.[18] Collectively, these preclinical studies showed the triagonist of incretin components has anti-obesity and anti-diabetes potential.

GLP-1 and PYY

PYY is secreted with GLP-1 in the L cells of the distal gut after nutrient ingestion to reduce appetite and food intake. GLP-1 and PYY bind to GLP-1R and neuropeptide Y2-receptor, respectively.[19,20] Both receptors are found in the arcuate nucleus of the hypothalamus, dorsal vagal complex, nucleus tractus solitarii, area postrema and nodose ganglion of the vagus nerve.[21,22] When PYY and GLP-1 were administered together intravenously to fasted humans, energy intake was reduced and activity in several areas of the brain involved in response to satiety increased.[23] Co-administration of both peptides to humans induced pre-meal insulin secretion.[24] Preclinical studies in mice showed that systemic co-administration of PYY and Exendin-4, a long acting GLP-1, synergistically decreased appetite and food intake independent of the GLP-1R signaling pathway.[25] In clinical and preclinical studies, the combination of GLP-1 and PYY demonstrated anti-obesity effects.

GLP-1 and other combinations

Several other combinations, including leptin, calcitonin, naltrexone, cholecystokinin (CCK) or gastrin with GLP-1, have been investigated for anti-obesity and anti-diabetic effects. CCK is a typical gastrointestinal hormone that promotes satiety after eating. When CCK is infused with GLP-1 to healthy humans, hunger feelings were synergistically reduced before meals.[26] Leptin is an anorectic hormone secreted by WAT by binding to the leptin receptor. Intraperitoneal co-administration of GLP-1 and leptin significantly reduced food intake in rats by transmitting the anorectic signal *via* the ascending neural pathway from the hindbrain.[27] The combination of Exendin-4 and leptin showed an additive effect on food intake reduction.[28] Naltrexone is an opioid antagonist acting on the reward system. The combination of naltrexone and Exendin-4 synergistically suppressed food intake in a dose-dependent manner and resulted in a rapid acquisition of a conditioned taste aversion.[29] Amylin is a pancreatic peptide co-secreted with insulin and involved in the control of satiety signaling. The combination of Exendin-4 and an amylin analog, salmon calcitonin, elicited a synergistic effect on reducing food intake and produced body weight loss in monkeys.[30] Gastrin is a peptide hormone secreted primarily by G cells in response to food ingestion and acts on its receptor, cholecystokinin B receptor, to exert physiological actions in the colon, pancreas, small intestine, liver, esophagus and kidney.[31] The combined administration of Exendin-4 with gastrin to diabetic db/db mice promoted β cell proliferation and differentiation, thereby maintaining the mass of β cells.[32] Combination therapy with GLP-1 and gastrin restored normoglycemia in non-obese diabetic mice by increasing the pancreatic β cell mass and downregulating the autoimmune response.[33]

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CONCLUSION

Many recent reports demonstrated that synergism with GLP-1 pharmacology, in contrast to existing monotherapies, has provided distinct novel strategies to combat multiple mechanisms simultaneously. Most of the current literature on GLP-1 combination therapies focused only on food intake. Only a few studies investigated the effect of GLP-1 combination therapy on energy expenditure, another major mechanism underlying obesity treatment. The role of GLP-1 combination therapy on energy expenditure should be clarified in future studies. Novel GLP-1 combination strategies with other anti-obesity and anti-diabetic hormones or drugs could produce more diverse multifunctional, targeted therapeutics. Through these efforts, GLP-1-based combination strategies will provide diverse therapeutic options and open a new era for personalized obesity and diabetes treatments.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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