Pharmacology & Therapeutics 239 (2022) 108187

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Regulation of feeding and therapeutic application of bioactive peptides

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ARTICLE INFO

Available online 14 April 2022

Editor: S.J. Enna

Keywords:
Obesity
Appetite
Peptide
Hypothalamus
Anti-obesity drug

ABSTRACT

Obesity and obesity-related diseases, such as diabetes mellitus and dyslipidemia, are worldwide pandemics; therefore, studies have been conducted energetically to elucidate the mechanism of obesity and develop anti-obesity drugs. Robust progress in the peptide chemistry and molecular biology has identified many peptides that regulate appetite and energy metabolism over the past dozen years. Several drugs, such as analogs or receptor agonists of anorectic peptides, have been developed. Overall, peptide-related drugs have powerful anti-obesity effects with fewer adverse effects than previous anti-obesity drugs. Liraglutide, a glucagon-like peptide-1 receptor agonist, was first used as an antidiabetic drug, and then high-dose liraglutide was used as an anti-obesity drug. Several candidates have been developed to explore their anti-obesity effects. Additionally, hybrid peptides consisting of two or more peptide sequences with strong anorectic effects have been designed. Here, we review peptides that are important for feeding regulation in terms of their mechanisms of action, interactions, and clinical application as anti-obesity drugs.

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Abbreviations: ACTH, adrenocorticotropic hormone; α-MSH, alpha-melanocyte-stimulating hormone; BMI, body mass index; CTR, calcitonin receptor; DIO, diet-induced obese; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; GHS-R, growth hormone secretagogue receptor; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; GOAT, ghrelin *O*-acyltransferase; GPCR, G-protein-coupled receptor; GSIS, glucose-stimulated insulin secretion; HFD, high-fat diet; ICV, intracerebroventricular; KO, knockout; LEAP2, liver-expressed anti-microbial peptide 2; LHA, lateral hypothalamic area; MCR, melanocortin receptor; NMU, neuromedin U; NMUR, neuromedin U receptor; NT, neurotensin; NTR, neurotensin receptor; NTS, solitary tract nucleus; NURP, neuromedin U precursor-related peptide; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus; RAMP, receptor activity-modifying protein; RYGB, Roux-en-Y gastric bypass; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; VTA, ventral tegmental area..

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https://doi.org/10.1016/j.pharmthera.2022.108187
0163-7258/

1. Introduction

The year 2021 is the 100th anniversary of the discovery of insulin. Over the past century, many peptides have been identified, and advances in genetic modification technology and peptide chemistry have facilitated the elucidation of their physiological activities and mechanisms of action. Various peptides have been investigated as potential treatment targets. To date, approximately 80 peptides have been used practically. More than 150 peptides are being applied clinically, and 400–600 peptides have been preclinically studied (Muttenthaler, King, Adams, & Alewood, 2021). In addition to peptide formulations for injection, oral and nasal formulations have been developed.

In recent years, obesity and associated metabolic diseases, such as diabetes mellitus (DM), dyslipidemia, and hypertension, have become prevalent worldwide and represent a major social problem. To address this challenge, anti-obesity drugs have been developed and clinically used. To develop safer and more effective anti-obesity drugs, intensive efforts have been made to elucidate the mechanisms that regulate food intake and energy metabolism. Although the basic feeding regulatory mechanism is similar in humans and wild animals, humans have a higher-order system called the hedonic feeding regulatory mechanism, which is more active in obese people (Rossi & Stuber, 2018). Appetite is mainly regulated by the hypothalamus and brainstem in the central nervous system, which forms a network to express many appetite-enhancing or appetite-suppressing substances. The appetite-enhancing substances produced in peripheral tissues include ghrelin from the stomach and asprosin from adipocytes (Duerrschmid et al., 2017). In contrast, most other substances produced in peripheral tissues are appetite-suppressing substances, such as leptin from adipose tissues and glucagon-like peptide-1 (GLP-1) from the small intestine. The hypothalamus receives homeostatic regulatory signals from peripheral tissues and hedonic regulatory signals from the upper central nervous system, including the limbic system (Hope, Tan, & Bloom, 2018). These signals are integrated to determine feeding behavior. Additionally, inflammation associated with obesity, intestinal microflora, synaptic plasticity, body temperature, and circadian rhythms affects appetite regulation (Browning, Verheijden, & Boeckxstaens, 2017; Torres-Fuentes, Schellekens, Dinan, & Cryan, 2017).

To develop anti-obesity drugs, it is important to understand the regulatory mechanism for feeding, apply it, and discover the modes of action associated with as few adverse drug reactions as possible. We selected eleven peptides whose effects and underlying mechanisms to regulate feeding have been elucidated substantially and clinical potentials have been demonstrated or expected to be done in the near future. This review describes these eleven important peptides that participate in appetite and body weight regulation.

2. Ghrelin

Ghrelin is a 28-amino acid peptide that was identified in 1999 as an endogenous ligand for the growth hormone secretagogue receptor (GHS-R) (Kojima et al., 1999). Ghrelin is mainly produced in the gastric endocrine cells. Ghrelin-producing cells account for 20–25% of endocrine cells in the gastric corpus and are the second most common cell type after enterochromaffin-like cells. Ghrelin mRNA has also been detected by RT-PCR in a wide range of peripheral organs and the brain (Date et al., 2000; Gnanapavan et al., 2002; Korbonits et al., 2001). In ghrelin, the third amino acid, serine, is esterized with *n*-octanoic acid. The acylated form of ghrelin is defined as ghrelin. Des-acyl ghrelin is a major molecular form that lacks fatty acid modifications and accounts for approximately 80–90% of the ghrelin moiety in the blood. Ghrelin has been identified in many mammals, birds, amphibians, and fish and has an acylation at the third amino acid, serine or threonine. Ghrelin acylation is mediated by ghrelin *O*-acyltransferase (GOAT), a lipid acyl transferase expressed on the membranes of ghrelin-producing cells (Gutierrez et al., 2008; Yang, Brown, Liang, Grishin, & Goldstein, 2008). GHS-R is expressed in various peripheral organs and widespread regions of the brain (Laviano, Molfino, Rianda, & Rossi Fanelli, 2012).

Ghrelin secreted from the stomach binds to the ghrelin receptor which is produced in the vagal ganglion cell body and axially transported to the end of the afferent fiber in the stomach (Date et al., 2002; Sakata et al., 2003). Ghrelin suppresses the electrical activity of the vagal afferent nerve. This electrical signal is transmitted to the solitary tract nucleus (NTS) of the medulla oblongata and subsequently relayed to the arcuate nucleus of the hypothalamus via noradrenergic neurons (Date et al., 2006). Ghrelin signaling activates neuropeptide Y/agouti-related protein neurons and inhibits pro-opiomelanocortin (POMC) neurons, eventually stimulating homeostatic feeding (Nakazato et al., 2001). Another possibility of ghrelin to act in the brain is that ghrelin, at least in part, can cross the blood-brain barrier to increase food intake (Uriarte et al., 2019) Functional magnetic resonance imaging tests have revealed the activation of regions involved in the reward system (amygdala, orbitofrontal cortex, substantia nigra, caudate nucleus, and hippocampus) after ghrelin administration in humans; thus, ghrelin may also enhance hedonic feeding through the limbic system (Malik, McGlone, Bedrossian, & Dagher, 2008).

In addition to its growth hormone secretion and orexigenic activities, ghrelin has multifaceted roles, such as promoting gastric juice secretion and gastrointestinal peristalsis, decreasing blood pressure, increasing cardiac output, and affecting metabolism, immunity, respiratory organs, learning, memory, fat accumulation, depression, and sleep (Kaiya, Miyazato, & Kangawa, 2011; Kaiya, Miyazato, Kangawa, Peter, & Unniappan, 2008; Nakazato et al., 2001; Takaya et al., 2000; Tschöp, Smiley, & Heiman, 2000; Wren et al., 2001). Basal plasma ghrelin levels are negatively correlated with body mass index (BMI). Because ghrelin increases food intake, ghrelin production (gastric ghrelin mRNA) is decreased in obesity by negative feedback. Blood ghrelin levels are high during fasting and rapidly decrease after meals (Shiiya et al., 2002; Ueno, Shiiya, Mizuta, Mondal, & Nakazato, 2007). Although the number of ghrelin-producing cells was comparable for obese individuals and healthy controls, the mRNA expression of ghrelin and GOAT was increased in obese patients (Castorina et al., 2021). Des-acyl ghrelin has been reported to enhance feeding, inhibit cell death in cultured myocardial cells, promote fat production in the bone marrow, inhibit glycerol release in peritesticular adipocytes, and inhibit cell proliferation in prostate cancer cells (Toshinai et al., 2006). Des-acyl ghrelin does not bind to GHS-R; however, its receptor or target molecule has yet to be identified.

Ghrelin has been investigated in clinical studies of cardiac failure, chronic obstructive pulmonary disease, functional dyspepsia, and post-surgical status of gastrointestinal disease, anorexia nervosa, and diabetic polyneuropathy. Ghrelin administration to patients with cachexia associated with chronic obstructive pulmonary disease, cardiac failure, or cancer improved the quality of life by increasing food consumption and improving respiratory function and exercise tolerance (Garcia, Friend, & Allen, 2013). Ghrelin administration in patients with chronic lower respiratory tract infections exhibited a wide range of effects, including anti-inflammatory effects, such as the reduction in sputum volume and levels of neutrophils, interleukin-8, and tumor necrosis factor-α in the sputum, prolongation of the 6 min walk distance, and increase in food consumption and body weight (Kodama, Ashitani, Matsumoto, Kangawa, & Nakazato, 2008). The ghrelin receptor agonists RM-131 and TZP-102 to diabetic patients complicated with diabetic gastroparesis improved gastric emptying (Shin et al., 2013). Blood ghrelin levels decreased to approximately one-third of preoperative levels in patients who underwent gastrectomy. Ghrelin administration effectively increased energy intake, appetite, and body weight in patients who underwent gastrectomy (Takiguchi et al., 2016). In 2021, the ghrelin receptor agonist anamorelin (orally administered at 100 mg once a day) was launched to treat cancer-related cachexia in Japan. Anamorelin administration to patients with stage 3 and 4 non-small cell lung cancer for 12 weeks increased body weight 1.46 kg and 2.14 kg compared to placebo in two clinical trials. There were no

differences in handgrip strength between anamorelin and placebo in both trials (Temel et al., 2016). Several ghrelin receptor antagonists have been shown to reduce food consumption and body weight in obese mice (Asakawa et al., 2003; Maletinska et al., 2011), however, these antagonists have not been clinically applied as anti-obesity drugs in humans.

3. Liver-expressed antimicrobial peptide 2 (LEAP2)

LEAP2, a 40-amino acid peptide, was first identified in 2003 as an antimicrobial peptide predominantly expressed in the liver (Krause et al., 2003). LEAP2 is highly conserved in mammals. In 2018, LEAP2 was demonstrated to be an endogenous antagonist of GHS-R (Ge et al., 2018). LEAP2 has two disulfide bonds and is a cationic peptide, often recognized in antimicrobial peptides. Although ghrelin activates GHS-R at a 50% effective concentration (EC50) of 7.1 nM, LEAP2 inhibits ghrelin-induced GHS-R activation at an IC50 of 6.0 nM (Ge et al., 2018). The N-terminal region of LEAP2 is essential for GHS-R binding (Wang et al., 2019). In particular, a longer segment containing at least 1–12 N-terminal residues, but not the 1–8 N-terminal sequence, was reported to have increased binding potency and efficacy to GHS-R (M'Kadmi et al., 2019). LEAP2 is primarily expressed in the liver and small intestine. In humans and mice, serum LEAP2 levels are positively correlated with BMI contrary to ghrelin, and blood glucose levels. Because plasma ghrelin level does not change after LEAP2 administration, increased serum LEAP2 in obesity unlikely reduces ghrelin production directly. Serum LEAP2 levels markedly decreased while fasting and increased after meals (Mani et al., 2019). In humans, LEAP2 expression in the small intestine markedly increased after Roux-en-Y gastric bypass (RYGB) (Hagemann et al., 2021). These changes in blood levels are opposite to those observed for ghrelin. Fasting plasma levels and postprandial plasma levels of LEAP2 decreased 2 years after RYGB and 12–18 months after sleeve gastrectomy, respectively (Mani et al., 2019). Two years after RYGB LEAP2 levels in the cerebrospinal fluid were elevated in patients with bacterial meningitis (Sakai et al., 2021).

LEAP2 canceled the effects of ghrelin *in vivo*, including growth hormone secretion, feeding, blood glucose elevation, and body temperature reduction (Ge et al., 2018; Islam et al., 2020). However, LEAP2 did not affect des-acyl ghrelin-induced body temperature reduction (Islam et al., 2020). LEAP2 did not affect GHS-R knockout (KO) mice. The N-terminal region of LEAP2 promoted insulin secretion from human pancreatic islets, whereas its administration to healthy individuals did not change blood glucose levels (Hagemann et al., 2021). LEAP2 has not been reported as an anti-obesity drug.

Overweight or obese children aged 3–12 years had equivalent plasma ghrelin levels but lower plasma levels of des-acyl ghrelin and LEAP2 than normal weight children. Serum LEAP2 levels were negatively correlated with BMI z-scores (calculated considering sex and age) (Fittipaldi et al., 2020). Conversely, a study of 171 children aged 3–17 years reported no difference in serum LEAP2 levels between obese and non-obese children. In obese and non-obese children, serum LEAP2 levels were higher in girls than boys. Among girls, those who had undergone menarche had higher serum LEAP2 levels than those who had not. LEAP2 levels in girls were positively correlated with insulin and triglyceride levels but negatively correlated with ghrelin levels. In boys, LEAP2 levels were positively correlated with leptin levels (Barja-Fernandez et al., 2021). In growing children, LEAP2 may affect body weight and sex and other hormones.

4. POMC and α-melanocyte-stimulating hormone (α-MSH)

POMC is a 241-amino acid polypeptide. It is highly expressed in the hypothalamic arcuate nucleus and is a precursor of the adrenocorticotropic hormone (ACTH) and α-MSH, and the latter consists of the first 13 amino acids of ACTH (Nakanishi et al., 1979). α-MSH acts on melanocortin receptors (MC1R, MC3R, MC4R, and MC5R). MC4R is expressed in the brain and involved in the regulation of feeding. MC4R KO mice exhibit obesity, overeating, and hyperinsulinemia (Fan, Boston, Kesterson, Hruby, & Cone, 1997; Tallam, Stec, Willis, da Silva, & Hall, 2005).

Leptin acts on leptin receptors expressed on POMC neurons to increase α-MSH production. α-MSH binds to MC4R in the paraventricular nucleus (PVN) to reduce food intake, causing weight loss (Baldini & Phelan, 2019). MC4R agonists have been investigated as potential anti-obesity drugs. Early generation MC4R agonists faced problems during clinical application because of adverse events, such as increased pulse rate and blood pressure. Continuous subcutaneous administration of setmelanotide, an MC4R agonist, for 3 day to 12 obese individuals increased resting energy expenditure by 111 kcal/day and lowered the non-exercise respiratory quotient (Chen et al., 2015).

Overeating-related obesity, together with *POMC* mutations, has been reported to cause ACTH deficiency, red hair, and pale skin in early childhood (Krude et al., 1998). Therefore, setmelanotide is expected to be effective in treating obesity associated with overeating. Setmelanotide administration to 8 of 10 POMC-deficient patients and 5 of 11 leptin-deficient patients caused a weight loss of 10% or more of their original body weights after 1 year of treatment. No severe adverse events were observed (Clement et al., 2020). A study of the *MC4R* gene in 452,300 individuals identified 12 nonsense/frameshift variants and 49 missense variants. Individuals carrying gain-of-function variants of the *MC4R* gene had a lower BMI prevalence of obesity and incidence of type 2 DM (T2DM) and coronary artery disease (Lotta et al., 2019).

Lipocalin 2, a 25 kDa glycoprotein was originally identified as an adipocytokine secreted by adipocytes. It caused insulin resistance and had elevated blood levels in multiple rodent models of obesity (Yan et al., 2007). Lipocalin 2 is at least 10 times more highly expressed in osteoblasts than in adipocytes, and it regulates food intake via MC4R. Lipocalin 2 could cross the blood-brain barrier and bind to MC4R in the paraventricular and ventromedial neurons in the hypothalamus to inhibit food intake. Intraperitoneal administration of lipocalin 2 once daily for 16 weeks in wild-type mice and *db*/*db* mice reduced food consumption and body weight (Mosialou et al., 2017). Lipocalin 2 expression was markedly upregulated in mice with pancreatic cancer, thereby reducing food consumption. In lipocalin 2 KO mice and mice pretreated with MC4R antagonists, pancreatic cancer-induced cachexia-anorexia was inhibited (Olson et al., 2021). Lipocalin 2 is expected to be further investigated as a new target for treating obesity and cancer-induced cachexia.

5. Glucagon

Glucagon is a 29-amino acid peptide produced by the pancreatic α-cells. Glucagon is encoded by the proglucagon gene, which also encodes GLP-1, GLP-2, oxyntomodulin, and glicentin. The glucagon receptor, a G protein-coupled receptor (GPCR), is mainly expressed in the liver, adipose tissue, and muscles (Dunphy, Taylor, & Fuller, 1998; Svoboda, Tastenoy, Vertongen, & Robberecht, 1994). In pancreatic islets, the glucagon receptor is expressed in the majority of β-cells and some α- and δ-cells. Glucagon secretion is promoted by hypoglycemia, epinephrine, amino acids (especially arginine and alanine), acetylcholine, cyclic adenosine monophosphate, and glucose-dependent insulinotropic polypeptide (GIP), and suppressed by glucose, free fatty acids, ketone bodies, somatostatin, insulin, and GLP-1 (Briant, Salehi, Vergari, Zhang, & Rorsman, 2016). Glucagon promotes gluconeogenesis and inhibits glycolysis in the liver. Glucagon also promotes the secretion of insulin, growth hormone, and epinephrine, inhibits gastrointestinal movement, and increases the glomerular filtration rate and lipolysis in adipose tissue (Haedersdal, Lund, Knop, & Vilsboll, 2018). The glucagon tolerance test is used to evaluate insulin secretion capacity by measuring the serum levels of C-peptide during fasting and 6 min after intravenous administration of 1 mg glucagon (Scheen, Castillo, & Lefebvre, 1996).

A sandwich ELISA developed several years ago has shown that plasma glucagon levels in healthy subjects decreased after an oral glucose tolerance test, whereas they increased after a mixed meal tolerance test (Miyachi et al., 2017). Plasma glucagon levels after fasting were significantly higher in patients with T2DM (approximately 35 pg/mL) than in healthy subjects (approximately 20 pg/mL) (Ichikawa et al., 2019).

Intramuscular or subcutaneous glucagon administration has been used to restore blood glucose levels during hypoglycemia. Additionally, easy-to-use nasal formulations of glucagon have recently been used in clinical practice (Sherr et al., 2016). A meta-analysis showed that the effect of nasal administration of glucagon on hypoglycemia was comparable to that of intramuscular or subcutaneous injection (Pontiroli & Tagliabue, 2020).

The mechanisms by which glucagon inhibits food intake and reduces body weight have been extensively investigated. Glucagon bound to the glucagon receptor in the liver transmits an anorectic signal to the brainstem via vagus afferent nerves (Geary, Le Sauter, & Noh, 1993; Le Sauter, Noh, & Geary, 1991). These signals are then relayed to the hypothalamic arcuate nucleus (Weatherford & Ritter, 1988). When glucagon receptor-KO mice were fed a normal chow diet, they exhibited hyperglucagonemia, hypoglycemia, and pancreatic α-cell hyperplasia, whereas their body weights were comparable to those of wild-type mice. Conversely, the KO mice fed a high-fat diet (HFD) exhibited lower food consumption, lower weight gain, and better glucose tolerance than wild-type mice (Conarello et al., 2007; Gelling et al., 2003). Obese Zucker rats carrying the mutated leptin receptor gene exhibited suppressed glucagon secretion. When glucagon was administered to these rats, food consumption remained unchanged, but body weight decreased markedly (Chan et al., 1984). These findings suggest that glucagon reduces body weight by mechanisms dependent on and independent of food intake. Glucagon crosses the blood-brain barrier (Inokuchi, Oomura, Shimizu, & Yamamoto, 1986) and binds to glucagon receptor in the hypothalamus (Hoosein & Gurd, 1984). Central administered glucagon reduced food intake via protein kinase A/Ca^{+}-calmodulin-dependent protein kinase kinase β/AMP-activated protein kinase dependent pathways in the arcuate nucleus and inhibited hepatic glucose production (Mighiu et al., 2013; Quinones et al., 2015). In diet induced obese animals, anorectic action and hepatic glucose production inhibition of central glucagon were decreased. Hypothalamic glucagon resistance seems to be related to hyperglycemia and hyperphagia in diabetes and obesity (Mighiu et al., 2013; Quinones et al., 2015).

Glucagon was reported to increase energy expenditure in rodents and humans through several mechanisms (Chan et al., 1984; Davidson, Salter, & Best, 1957; Nair, 1987). Glucagon enhances energy expenditure and locomotor activity via fibroblast growth factor 21 (Habegger et al., 2013). Glucagon also increases the number of brown adipocytes and thermogenesis (Billington, Briggs, Link, & Levine, 1991; Doi & Kuroshima, 1982) which is mediated, at least partially, by fibroblast growth factor 21 (Beaudry et al., 2019; Kinoshita et al., 2014). However, glucagon-induced energy expenditure is independent of brown adipocytes in humans (Salem et al., 2016).

Dual agonists of the GLP-1 and glucagon receptors are promising for treating obesity and DM. Weekly administration of PEGylated dual agonists to diet-induced obese (DIO) mice reduced body fat, food consumption, and body weight and improved glucose tolerance (Fig. 1A) (Day et al., 2009). As described later (see the Leptin section), the weight-reducing effect of leptin is attenuated by obesity. However, a combination of one of the above dual agonists and leptin exerted a greater reduction in food consumption and body weight (Clemmensen et al., 2014). The clinical effects of three types of dual agonists of the GLP-1 and glucagon receptors have been reported. Patients with T2DM who were administered the first dual agonist, SAR425899, for 26 weeks exhibited decreased body weight and hemoglobin A1c (HbA1c) levels (Table 1). SAR425899 improved some indices of β-cell function assessment (Schiavon et al., 2021). In an *in vitro* assay, cotadutide (MEDI0382) activated the GLP-1 and glucagon receptors at a ratio of 5:1 (Henderson et al., 2016). Administration of cotadutide for 54 weeks to obese patients with T2DM decreased HbA1c levels and body weight and improved the serum lipid profiles, liver function, nonalcoholic fatty liver disease fibrosis score, and fibrosis-4 index (Nahra et al., 2021) (Table 1). Cotadutide further reduced inflammation and hepatic fibrosis compared with the GLP-1 receptor agonist liraglutide in a mouse model of nonalcoholic steatohepatitis (Boland et al., 2020). Overweight Chinese adults given a weekly subcutaneous formula LY3305677, a dual agonist of GLP-1 and glucagon receptors, for 12 weeks exhibited a weight loss of 3.4–5.4 kg (Ji et al., 2021).

A triagonist of GLP-1, GIP, and glucagon receptors reduced food consumption and body weight in DIO mice (Fig. 1B). Food consumption was comparable between the triagonist and co-agonist of GLP-1 and GIP receptors, whereas triagonist administration reduced body weight more than the co-agonist. The triagonist also improved insulin resistance, glucose tolerance, and hepatic fat levels, and increased energy expenditure in DIO mice (Finan et al., 2015). Another triagonist SAR441255 reduced body weight in DIO mice more effectively than GLP-1 receptor/glucagon receptor dual agonist. It also reduced postprandial plasma glucose levels in healthy humans (Bossart et al., 2022). Further studies are expected to be conducted on hybrid peptides to determine the optimal combination of anorectic peptides, such as GLP-1, GIP, glucagon, leptin, and other peptides, and the optimal combination balance between peptide titers to boost beneficial effects and reduce adverse events.

6. GLP-1

GLP-1 is a 30-amino acid peptide secreted by L-cells in the lower intestinal tract. GLP-1 is rapidly inactivated by dipeptidyl peptidase-4 (DPP-4) in the blood and vascular walls. The effects of GLP-1 include glucose-dependent enhancement of insulin secretion, suppression of glucagon secretion, inhibition of gastric emptying, promotion of glycogen synthase activity in the liver, and protection and proliferation of pancreatic β-cells (Holst, 2007). Additionally, GLP-1-derived signals reach the nodose ganglion via the vagus afferent nerve and activates neurons in the NTS of the medulla oblongata (Krieger, 2020; Nakabayashi, Nishizawa, Nakagawa, Takeda, & Niijima, 1996). GLP-1 then acts on the hypothalamus to inhibit food intake, preventing weight gain (Gutzwiller et al., 1999). GLP-1 is also expressed in the NTS of the medulla oblongata, from which nerve fibers extend into various sites in the brain, especially the hypothalamic arcuate and paraventricular nuclei (Katsurada & Yada, 2016). The GLP-1 receptor is co-expressed with ghrelin receptors in nodosa ganglion neurons (Zhang, Sakoda, & Nakazato, 2020). Moreover, the GLP-1 receptor is widely expressed in peripheral organs, such as the pancreatic islets, heart, kidneys, and gastrointestinal tract, and the central nervous system (Holst, 2007). Both central and peripheral GLP-1 administration suppressed food intake. When a balloon distended the stomach of rats, GLP-1-containing nerves in the NTS were activated, and food consumption decreased. However, pre-administration of a GLP-1 receptor antagonist into the fourth cerebral ventricle attenuated GLP-1-induced food intake reduction. GLP-1 receptors in the NTS perceive mechanical distension stimulation of the stomach to inhibit food intake (Hayes, Bradley, & Grill, 2009). GLP-1 produced in the gastrointestinal tract inhibits peristalsis of the stomach via the vagus nerve, increases the contractility of the pylorus, and inhibits gastric emptying. GLP-1 produced in the NTS inhibits gastric emptying and enhances colonic motility.

In 1992, exendin-4 (exenatide) was identified as a full agonist of the GLP-1 receptor (Eng, Kleinman, Singh, Singh, & Raufman, 1992; Raufman, Singh, Singh, & Eng, 1992). Because exendin-4 escapes cleavage by DPP-4, it was launched as an antidiabetic drug in the United States in 2005. Liraglutide is another GLP-1 analog that substitutes lysine at position 34 of human GLP-1 with arginine and connects lysine-26 with N-palmitoylglutamic acid. This modification enhances binding affinity for blood albumin, which inhibits cleavage by DPP-4, thereby

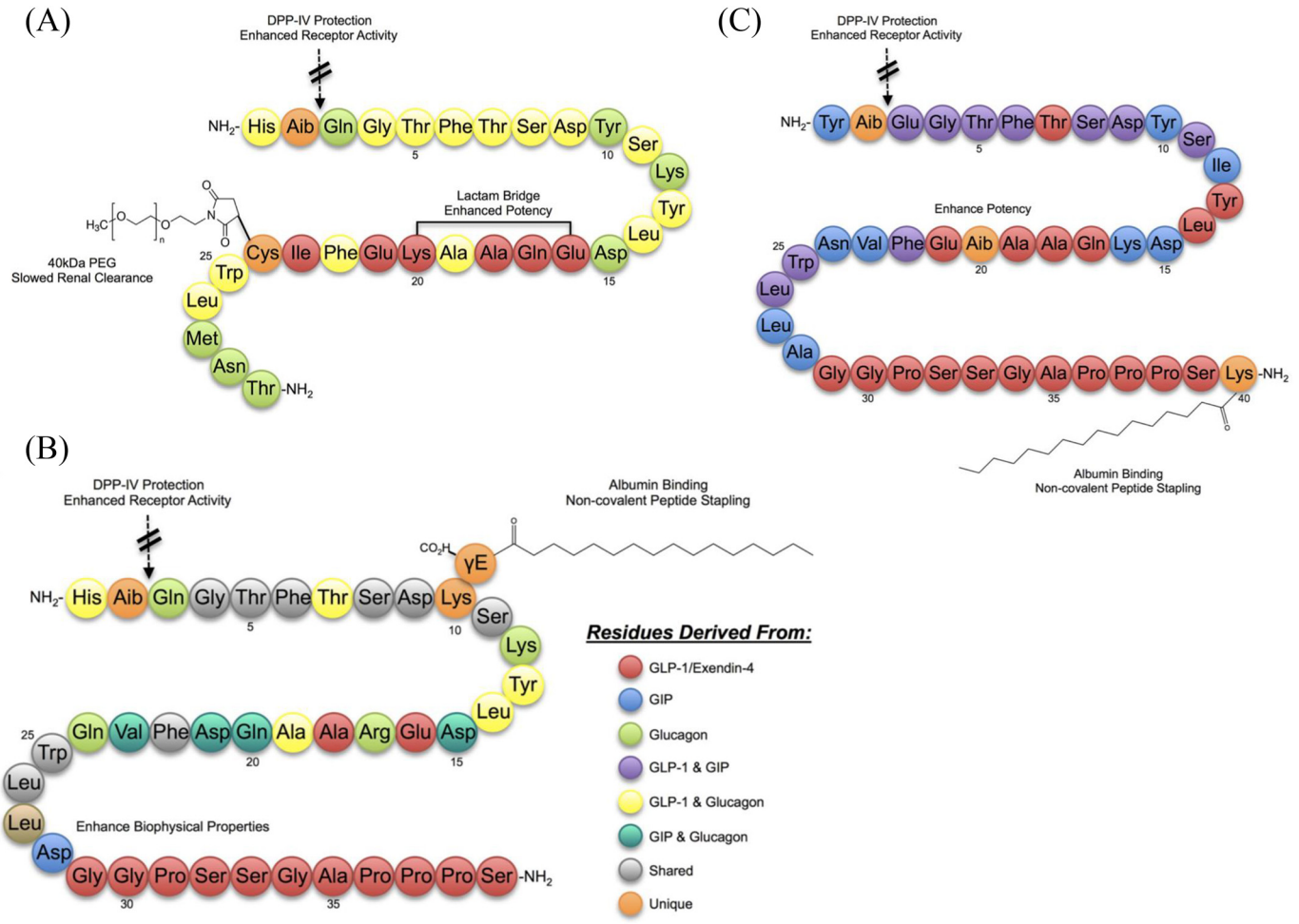

Fig. 1. Structure of glucagon receptor/GLP-1 receptor co-agonist, glucagon receptor/GLP-1 receptor/GIP-receptor triagonist, and GIP receptor/GLP-1 receptor co-agonist. These figures are cited from (Tschöp et al., 2016).
(A) Amino acid sequence of glucagon receptor/GLP-1 receptor co-agonist (Day et al., 2009). Residues derived from GLP-1 or exendin-4 are red; glucagon residues are green; residues shared between GLP-1 and glucagon are yellow; and unique residues are orange. Aib, aminoisobutyric acid. Additional chemical engineering, including an i, i+4 side-chain macrocyclization from residues Glu^{16} to Lys^{20} and a 40 kDa polyethylene glycol (PEG) moiety at Cys^{24}, is also represented with chemical structures.
(B) Amino acid sequence of glucagon receptor/GLP-1 receptor/GIP receptor triagonist (Finan et al., 2015). Residues derived from GLP-1 or exendin-4 are red, residues derived from GIP are blue, residues derived from glucagon are green, residues shared between GLP-1 and GIP are purple, residues shared between GLP-1 and glucagon are yellow, residues shared among all three native hormones are gray, and unique residues are orange. Aib, aminoisobutyric acid; γE, gamma-glutamic acid. A 16-carbon acyl chain (palmitoyl; 16:0) covalently attached via a γ-carboxylate spacer to the side-chain amine of Lys^{10} is represented by its chemical structure.
(C) Amino acid sequence of the acylated version of the GIP receptor/GLP-1 receptor co-agonist (Finan et al., 2013). Residues derived from GLP-1 or exendin-4 are red, those derived from GIP are blue, those shared between GLP-1 and GIP are purple, and unique residues are orange. Aib, aminoisobutyric acid. A 16-carbon acyl chain (palmitoyl; 16:0) covalently attached to the side-chain amine of Lys^{40} is represented by its chemical structure.

extending the duration of its activity. In the United States, liraglutide 3.0 mg/day was launched as an anti-obesity drug. In a double-blind comparative study in which non-diabetic obese patients were treated with liraglutide at 3.0 mg/day for 56 weeks, the percentage of patients with a weight loss of 10% or more was 33.1%; this was significantly higher than the 10.6% observed in the placebo group (Pi-Sunyer et al., 2015) (Table 1).

The nasal formulation of human GLP-1 increased insulin secretion, inhibited glucagon secretion, and increased 1,5-anhydroglucitol in patients with T2DM (Ueno et al., 2014). Oral semaglutide was approved by the United States in 2019. This drug was developed into an oral formulation with an oral absorption enhancer, salcaprozate sodium (sodium *N*-[8-(2-hydroxybenzoyl) amino] caprylate). The drug is orally administered with a small amount of water (< 120 mL) at least 30 min before breakfast. Administration of 7 mg/day of oral semaglutide to Japanese patients with T2DM for 26 weeks resulted in decreased HbA1c levels by 1.0–1.2% and body weight by 1.0–2.7%. A dose of 14 mg/day resulted in decreased HbA1c levels by 1.4–1.7% and body weight by 3.7–4.7% (Araki et al., 2021). In a double-blind study in which oral semaglutide was administered for a median duration of 15.9 months to patients with T2DM at high risk of cardiovascular events, cardiovascular mortality was significantly lower in the oral semaglutide group, with a hazard ratio of 0.49 (Husain et al., 2019) (Table 1). Oral formulations of other peptides could allow for the treatment of diabetes and the progression of obesity.

7. GIP

GIP is a 42-amino acid peptide and one of the incretin hormone. DPP-4 also inactivates GIP by cleaving the second alanine from the N-terminus. GIP is primarily secreted from K cells in the ileum; it is also produced in the mandibular salivary glands, stomach, and brain. In humans, plasma GIP levels are low under fasting conditions and increase five-fold or more after food intake in a meal-size-dependent manner (Morgan, Morris, & Marks, 1978; Ueno et al., 2018). GIP is secreted more after fat intake than carbohydrate intake (Baggio &

Table 1
Clinical trials for peptide agonists

Drugs	Subjects	n	Age	Duration of DM (years)	Period	HbA1c (%)		Body weight (kg)		Reference
						Basal	Δ	Basal	Δ	
Placebo	Overweight to obese T2DM	7	56.1		26 weeks	8.3	−1.2 §	89.7	−2.3 §	(Schiavon et al., 2021)
SAR 0.12~0.2 mg		46				8.1	−1.9 §*	92.9	−3.2 §	
Liraglutide 1.8 mg		17				8.0	−1.4 §*	103.9	−5.9 §	
Placebo	Overweight to obese T2DM (white 94–99%)	112	57.3	7.6	54 weeks	8.2	−0.45	98.1	−0.9	(Nahra et al., 2021)
Cotadutide 100 μg		100	57.6	7.5		8.1	−1.03 *	99.0	−3.2 *	
Cotadutide 200 μg		256	57.3	7.7		8.2	−1.16 *	98.1	−3.1 *	
Cotadutide 300 μg		256	56.3	7.6		8.1	−1.19 *	100.8	−4.4 * #	
Liraglutide 1.8 mg		110	55.5	7.6		8.1	−1.17 *	102.1	−2.9 *	
Placebo	Obesity without DM (white 85%)	1,244	45.0	–	56 weeks	5.6	−0.06	106.2	−2.8	(Pi-Sunyer et al., 2015)
Liraglutide 3.0 mg		2,487	45.2	–		5.6	−0.3 *	106.2	−8.4 *	
Placebo	T2DM (white 72%, Asian 20%)	1,592	66.0	15.1	15.9 months	8.2	−0.3	90.8	−0.8	(Husain et al., 2019)
Oral semaglutide		1,591	66.0	14.7		8.2	−1.0 *	91.0	−4.2 *	
Placebo	Overweight to obese T2DM (white 73%)	36	54.6	7.6	12 weeks	8.2	−0.2	89.9	−1.1	(Frias et al., 2017)
NNC		37	54.7	8.5		8.4	−1.4 *	91.8	−2.6 *	
Liraglutide 1.8 mg		35	55.2	7.8		8.4	−1.5 *	90.9	−2.2	
Insulin glargine	Overweight to obese T2DM (white 82%)	1,000	63.8	10.7	52 weeks	8.5	−1.4	90.2	1.9	(Del Prato et al., 2021)
Tirzepatide 5 mg		329	62.9	9.8		8.5	−2.2 †	90.3	−7.1 †	
Tirzepatide 10 mg		328	63.7	10.6		8.6	−2.4 †	90.6	−9.5 †	
Tirzepatide [15] mg		338	63.7	10.4		8.5	−2.6 †	90.0	−11.7 †	

SAR; SAR425899
T2DM; type 2 diabetes mellitus
NNC; NNC0090-2746
* P<0.05 vs placebo
§ P<0.05 vs pre-treatment
# P<0.05 vs liraglutide
† P<0.05 vs insulin glargine

Drucker, 2007). The GIP receptor is a GPCR widely expressed in pancreatic α and β-cells, the gastrointestinal tract, and the brain (Usdin, Mezey, Button, Brownstein, & Bonner, 1993).

GIP enhances glucose-dependent insulin secretion (Dupre, Ross, Watson, & Brown, 1973) and stimulates glucagon secretion at euglycemia in healthy human (Meier et al., 2003). GIP does not inhibit gastric emptying unlike GLP-1 (Meier et al., 2004). GIP also plays a role in bone remodeling and fat accumulation (Beck & Max, 1986; Nauck & Meier, 2018). GIP activates lipoprotein lipase (Kim, Nian, & McIntosh, 2007, 2010) and promotes the uptake of fatty acids and glucose (Beck & Max, 1986; Hauner, Glatting, Kaminska, & Pfeiffer, 1988). It promotes fat synthesis in cultured adipocytes (Hauner et al., 1988). In humans, GIP increases blood flow and triglyceride uptake in adipose tissues (Asmar et al., 2017). In T2DM, GLP-1-induced glucose-dependent insulin secretion is preserved, but GIP-induced glucose-dependent insulin secretion is attenuated (Meier et al., 2001; Nauck et al., 1993; Vilsboll, Krarup, Madsbad, & Holst, 2002).

GIP has been reported to increase body weight in many investigations. GIP receptor antagonists, vaccination with GIP, monoclonal antibodies against GIP receptors, and GIP receptor-KO mice resulted in less weight gain than their respective control groups, especially in HFD (Boylan, Glazebrook, Tatalovic, & Wolfe, 2015; Fulurija et al., 2008; McClean et al., 2007; Miyawaki et al., 2002). Patients carrying loss-of-function mutations in the GIP or GIP receptor genes are unlikely to gain body weight (Turcot et al., 2018). Co-administration of GLP-1 and GIP attenuated the anorexigenic effect of GLP-1 in obese individuals (Bergmann et al., 2019). GIP addition to patients given chronic liraglutide treatment worsened postprandial plasma glucagon, serum lipid, and plasma glucose levels (Bergmann et al., 2020). Based on these results, GIP alone has not been used as a therapeutic drug for T2DM.

However, the effects of GIP on body weight remain controversial. Overexpression of GIP in HFD-induced obese mice resulted in weight loss and decreased blood glucose levels (Kim et al., 2012). When the GIP analog ZP4165 was administered to HFD-induced obese mice, their body weights remained unchanged, whereas co-administration of the GIP analog with liraglutide significantly reduced body weights and food intake compared with the mice given liraglutide alone (Norregaard et al., 2018). Although both GIP receptor agonists and antagonists have been reported to cause weight loss as mentioned above, their mechanisms are gradually elucidated. Chronic GIP receptor agonism using a long-acting-GIP receptor agonist desensitizes GIP receptor activity and functions like a GIP receptor antagonist in adipocytes and adipose tissue (Killion et al., 2020).

GIP receptors in the brain could inhibit food intake. In the brain, GIP receptors are expressed in the arcuate, dorsomedial, and paraventricular nuclei of the hypothalamus in both humans and mice. Activation of GIP receptors in the hypothalamus inhibits food intake, which is not additive to concomitant GLP-1 receptor activation (Adriaenssens et al., 2019). GIP receptor deficiency in the brain of HFD-fed mice resulted in less body weight gain and better glucose tolerance. Additionally, central administration of fatty acyl-GIP to HFD-fed mice reduced body weight compared to control and liraglutide-treated mice. Peripheral administration of fatty acyl-GIP to HFD-fed mice also reduced body weights (Zhang, Delessa et al., 2021).

Some hybrid compounds of GLP-1 and GIP have been used in basic and clinical studies. Co-agonists of GLP-1 and GIP receptors reduced blood glucose levels and body fat mass in obese animals more than selective GLP-1 receptor agonists (Finan et al., 2013). GIP receptor antagonist antibodies conjugated to GLP-1 receptor agonist reduced body weight and improved glucose and fat metabolism in obese mice and monkeys (Lu et al., 2021). The administration of NNC0090-2746, a dual agonist of GLP-1 and GIP receptors, to patients with T2DM reduced HbA1c levels and body weight (Frias et al., 2017) (Table 1). Chronic administration of tirzepatide (LY3298176) (Fig. 1C), a once-weekly formulation of dual GLP-1 and GIP receptor agonist, to mice significantly reduced HbA1c levels and body weights compared with GLP-1 receptor

agonists (Coskun et al., 2018). Treatment with tirzepatide delayed gastric emptying, similar to GLP-1 receptor agonists (Urva et al., 2020). A 52-week administration of tirzepatide to patients with T2DM reduced HbA1c levels and body weights in a dose-dependent manner (Del Prato et al., 2021) (Table 1).

8. Neuromedin U (NMU)

NMU is a 23–25-amino acid neuropeptide (Fig. 2), which was first isolated from the spinal cord of pigs in 1985, and later from other species (Minamino, Kangawa, Honzawa, & Matsuo, 1988; Minamino, Kangawa, & Matsuo, 1985). It was named based on its powerful contractile activity in the rat uterine muscle. NMU is widely expressed in the central nervous system and peripheral tissues and has emerged as a new player in regulating appetite control, stress response, energy metabolism, inflammation, and glucose homeostasis (Fig. 3) (Malendowicz & Rucinski, 2021; Mitchell, Maguire, & Davenport, 2009; Nakazato et al., 2000; Peier et al., 2011; Teranishi & Hanada, 2021). NMU has two cognate GPCRs, NMU receptor 1 (NMUR1) and NMUR2 (Mitchell et al., 2009). NMUR1 is predominantly distributed in peripheral tissues, particularly in the gastrointestinal tract, lungs, immune system, and pancreas, whereas NMUR2 is abundant in the hypothalamus, hippocampus, and spinal cord. NMU and NMUR2 are primarily produced in the arcuate and paraventricular nuclei in the hypothalamus (Teranishi & Hanada, 2021).

Intracerebroventricular (ICV) administration of NMU in rats and mice reduced food intake and body weight and increased energy expenditure and thermogenesis (Hanada et al., 2003; Howard et al., 2000; Ivanov, Lawrence, Stanley, & Luckman, 2002; Kojima et al., 2000; Nakazato et al., 2000; Niimi, Murao, & Taminato, 2001). Direct microinjection of NMU into the rat PVN reduced food intake and increased locomotor activity (Novak, Zhang, & Levine, 2006; Wren et al., 2002). NMU-overexpressing transgenic mice are leaner and hypophagic (Kowalski et al., 2005), whereas *Nmu* KO mice exhibit obesity, reduced locomotor activity, energy expenditure, hyperinsulinemia, and hyperlipidemia (Hanada et al., 2004). Intriguingly, knockdown of *Nmur2* in the PVN of rats fed an HFD increased food intake and body weight gain (Benzon et al., 2014). ICV administration of NMUR2 agonist EUK2010 reduced body weights in rodents (Fang, Zhang, Li, Dong, & Hu, 2006).

NMU also has peripheral actions that regulate feeding behavior and energy homeostasis. Subcutaneous acute or chronic administration of NMU to mice reduced food intake, lowered body weight, and increased core body temperature, metabolic rate, and plasma levels of the anorectic peptides GLP-1 and peptide YY. These effects were abolished in *Nmur1* KO mice, suggesting the involvement of the NMUR1 signaling pathway in the peripheral control of energy balance (Peier et al., 2011). An increasing interest in the role of NMU concerns the regulation of pancreatic β-cell function and maintenance (Fig. 4). NMU and NMUR1 mRNA have been identified in the pancreatic islets of humans and rodents and β-cell-derived MIN6-K8 cells (Kaczmarek et al., 2006; Rucinski et al., 2007; Zhang et al., 2017). NMU and NMUR1 agonist 6a suppressed glucose-stimulated insulin secretion (GSIS) (Alfa et al., 2015; Kaczmarek et al., 2006; Kaczmarek et al., 2009; Zhang et al., 2017). In contrast, *Nmu* knockdown in MIN6-K8 cells elevated GSIS. These results suggest that NMU directly acts on β cells through NMUR1 in an autocrine or paracrine manner (Zhang et al., 2017). NMU produced in the proximal intestine suppressed GSIS in a human islet perfusion assay (Alfa et al., 2015). However, another study using isolated perfused rat pancreas and small intestine failed to detect the insulinostatic effect of NMU administered into blood vessels (Kuhre et al., 2019). The discrepancy of the effects of NMU on insulin secretion could be caused by different administration routes (ICV, subcutaneous or intravenous), animal condition (mouse or rat, the strain used, obese or not), or experimental protocol (NMU dose or administration duration). A recent study added a new role of NMU on β-cell maintenance (Fig. 4) (Zhang et al., 2020). NMU induced mitochondrial dysfunction by impairing mitochondrial biogenesis, respiration, and mitochondrial Ca^{2+} uptake in β-cells, causing endoplasmic reticulum (ER) stress. In contrast, *Nmu* knockdown in β-cells increased the number of insulin granules and improved mitochondrial biogenesis and function. NMUR1 in β-cells is coupled to $G\alpha_{i2}$ and $G\alpha_o$ to reduce intracellular Ca^{2+} influx and cyclic adenosine monophosphate levels. NMU was upregulated in both islets of *db*/*db* mice and palmitate-treated β-cells. Under diabetic conditions, upregulation of NMU could suppress insulin secretion by inducing mitochondrial dysfunction and ER stress, contributing to subsequent β-cell dysfunction (Zhang et al., 2021).

Two *NMU* mutations are associated with the onset of human obesity. One was located in the signal peptide of preproNMU (NMU Ala19Glu) in middle-aged Caucasians, which was expected to reduce NMU export. The other is NMU Arg165Trp, found in a Czech family, which causes hypertriglyceridemia and childhood-onset obesity (Hainerova et al., 2006).

New NMU analogs with longer half-lives have been developed to treat obesity, such as polyethylene glycol-, human serum albumin-, and palmitate-conjugated NMU (Dalboge et al., 2015; Ingallinella et al., 2012; Neuner et al., 2014). However, these NMU analogs are not NMUR1- or NMUR2-selective, and their effectiveness is too weak to treat obesity. Therefore, PEGylated NMU-8 (Inooka et al., 2017), a PEGylated NMUR2-selective agonist (Kanematsu-Yamaki et al., 2017), alkylated NMU-8, and an alkylated NMUR1-selective agonist were synthesized (Nagai et al., 2018). Only the NMUR2-selective agonist exhibited greater efficacy in reducing body weight and food intake and relatively fewer adverse effects in DIO mice. More recently, intranasal administration of NMUR2-selective agonists (CPN-116 and CPN-221) reduced body weight and food intake in mice (Takayama et al., 2020; Tanaka et al., 2020).

PreproNMU produces another peptide, NMU precursor-related peptide (NURP) (Mori et al., 2017). The authors deduced the NURP structure based on dibasic amino acid bonds in preproNMU (Fig. 2). NURPs consist of two peptides containing 33 and 36 residues (designated NURP33 and NURP36, respectively). NURP immunoreactivity was abundant in the pituitary gland and small intestine and detected in the brain of rats (Mori et al., 2017). ICV administration of NURP33 to mice increased their metabolic rate and caused a short-term (~4 h) increase in feeding (Bechtold, Ivanov, & Luckman, 2009). ICV administration of both NURP33 and NURP36 to rats exerted NMU-like sympathetic nerve effects, including increased locomotor activity, energy expenditure, heart rate, and thermogenesis, but NURP33 did not reduce food intake (Ensho et al., 2017). NURP increased prolactin release from the pituitary gland by activating dopaminergic neurons in the hypothalamus (Mori et al., 2017; Nakahara et al., 2020). Neither NURP33 nor NURP36 activated the two NMU receptors, and NURP did not reduce food intake (Ensho et al., 2017; Nakahara et al., 2020). Further studies are needed to identify the cognate receptor for NURP and functional interactions between NMU and NURP.

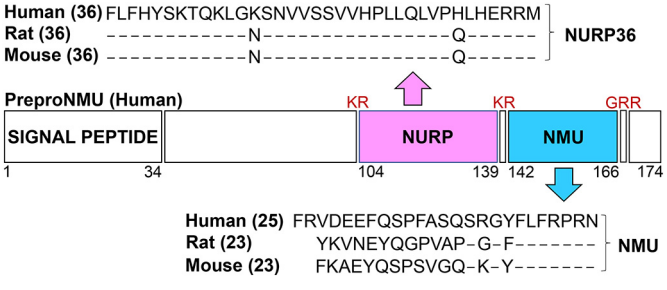

Fig. 2. Amino acid sequences of preproNMU. Data in the schematic structure are from Protein Knowledgebase (UniProtKB) P48645. Hyphens in rat and mouse sequences indicate the same amino acids as humans. Numbers in parentheses represent the total number of amino acids. NURP33 is a peptide that lacks the C-terminal RRM from NURP36. K, lysine; R, arginine; G, glycine.

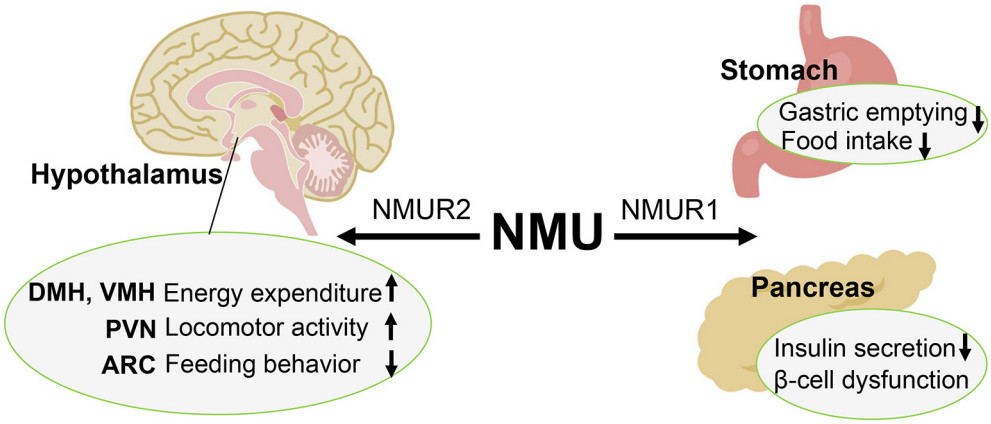

Fig. 3. NMU in energy homeostasis. NMU acts centrally via NMUR2 to increase energy expenditure and locomotor activity, and to decrease homeostatic feeding behavior. NMU also acts peripherally via NMUR1 to decrease gastric emptying, food intake and to suppress insulin secretion. ARC, the arcuate nucleus; DMH, the dorsomedial hypothalamic nucleus; PVN, the paraventricular nucleus; VMH, the ventromedial hypothalamus.

9. Neurotensin (NT)

NT is a 13-amino acid peptide secreted from the jejunum and ileum after food intake (Goedert & Emson, 1983). It is also produced in the entorhinal cortex, hippocampus, hypothalamus, and ventral tegmental area (VTA) of the brain (Satoh & Matsumura, 1990; Uhl, Goodman, & Snyder, 1979). NT has three cognate receptors (NTR1–3) (Vincent, Mazella, & Kitabgi, 1999). NT stimulates fat absorption from the intestine and is involved in regulating blood pressure, secretions of corticotropin-releasing hormone and adrenocorticotropic hormone, sleep and wakefulness, and body temperature (Bissette, Nemeroff, Loosen, Prange Jr., & Lipton, 1976; Fitzpatrick et al., 2012; Li et al., 2016; Rioux et al., 1981; Rowe, Viau, Meaney, & Quirion, 1995). Blood pro-NT levels are associated with the incidence of obesity, T2DM, dyslipidemia, cardiovascular disease, breast cancer, chronic kidney disease, nonalcoholic fatty liver disease, and overall morality caused by cardiovascular issues (Barchetta et al., 2018; Januzzi Jr. et al., 2016; Melander et al., 2012). In longitudinal studies conducted in the United States, Germany, and Sweden, blood levels of NT and pro-NT were positively correlated with the development of insulin resistance, obesity, metabolic syndrome, and all causes of mortality in patients with chronic kidney disease (Li et al., 2016; Nicoli et al., 2021; Tonjes et al., 2020).

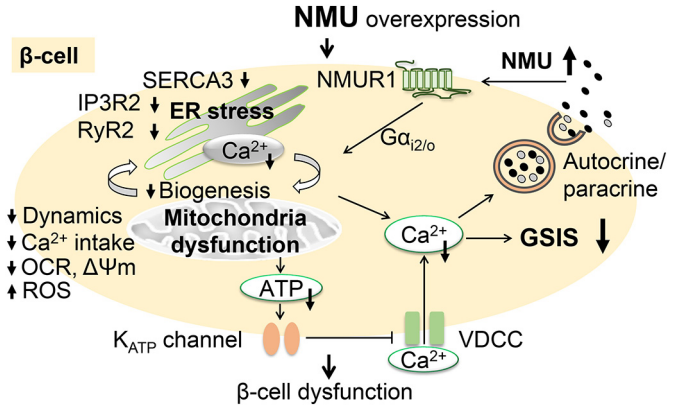

Fig. 4. Schematic illustration of NMU's roles in β-cell dysfunction. NMU acts directly on β-cells through NMUR1 coupled with $G\alpha_{i2/o}$. NMU causes mitochondrial dysfunction and induces ER stress. Decreased intracellular ATP and Ca^{2+} levels hamper GSIS to cause β-cell dysfunction, which may lead to further pathological development of type 2 diabetes. ER, endoplasmic reticulum; GSIS, glucose-stimulated insulin secretion; IP3R2, inositol triphosphate receptor 2; OCR, oxygen consumption rate; ROS, reactive oxygen species, RyR2, ryanodine receptor 2; SERCA3, sarco/endoplasmic reticulum Ca^{2+}-ATPase type 3; ΔΨm, mitochondrial membrane potential.

Direct injection of NT into mouse and rat brains reduced food consumption (de Beaurepaire & Suaudeau, 1988; Hawkins, Barkemeyer, & Tulley, 1986). NTR1 KO mice exhibited increased food consumption and weight gain (Kim, Leckstrom, & Mizuno, 2008; Opland et al., 2013). Sleeve gastrectomy in NTR1 KO mice was less effective in the reduction of food consumption, and especially fat intake and body fat mass (Ratner et al., 2021). Lateral hypothalamic area (LHA) NT KO mice showed increased body fat mass and decreased locomotor activity, energy expenditure, water intake, and orexin expression in the LHA (Brown et al., 2018). Administration of clozapin-N-oxide, a chemogenetic inhibitor of NT neurons, to LHA reduced NT expression and the anorectic effect of leptin (Brown et al., 2018). Furthermore, the VTA contains dopaminergic neurons that express NTR1. NT increased dopamine release, thereby reducing food consumption and increasing locomotor activity (Perez-Bonilla et al., 2021; Vadnie et al., 2014)

Peripheral administration of NT activates the brainstem, hypothalamus, and area postrema. After vagotomy, the inhibitory effect of the peripheral administration of NT on food intake remained, but the duration of the effect was shorter (Ratner et al., 2016). Thus, NT appears to inhibit food intake via both the vagus nerve and bloodstream. The half-life of NT in rodents is 30 sec (Aronin, Carraway, Ferris, Hammer, & Leeman, 1982). Intraperitoneal administration of long-acting pegylated NT to mice increased POMC mRNA expression in the hypothalamus. Although native NT inhibited food intake for up to 1 h after administration, pegylated NT reduced food intake 10 h after administration (Ratner et al., 2016). The subcutaneous administration of pegylated NT to high-fat and high-sucrose DIO mice reduced food consumption, body weight, and body fat mass. Pegylated NT failed to affect food intake or body weight in MC4R KO mice (Ratner et al., 2019). These findings revealed the importance of the melanocortin system on the inhibitory effect of NT on food intake.

NT, secreted from lymphatic endothelial cells in adipose tissues, activated extracellular signal-regulated kinase via NTR2 in brown adipocytes, and attenuated thermogenesis by reducing the expression of thermogenesis-related genes (Li et al., 2021). Low temperatures and norepinephrine from sympathetic nerves reduced the expression and secretion of NT. Overexpression of NT rendered mice intolerant to cold temperatures. In contrast, NT and NTR2 KO mice were tolerant to cold temperatures. Suppression of NTR2 expression in obese mice enhanced energy expenditure, increased expression of thermogenic genes, and slowed body temperature reduction after cold stimulation. Although food consumption remained unchanged, these mice exhibited less weight gain, decreased body fat mass, and improved glucose tolerance

and insulin resistance (Li et al., 2021). Thus, NTR2 antagonists could be potential candidates for anti-obesity drugs.

Although NTR1 agonists or NT reduced food consumption, they were unsuitable for anti-obesity drugs because of dangerous blood pressure and body temperature reduction (Fantegrossi, Ko, Woods, & Richelson, 2005; Feifel, Goldenberg, Melendez, & Shilling, 2010). The clinical application of NT agonists and antagonists has been attempted to treat schizophrenia and Parkinson's disease (Boules, Shaw, Fredrickson, & Richelson, 2007; Meltzer, Arvanitis, Bauer, Rein, and Meta-Trial Study, G, 2004; Mesnage et al., 2004). Activation of NTR1 alone in the VTA reduced body weight and food consumption, especially palatable food intake, but did not change blood pressure or body temperature (Perez-Bonilla et al., 2021).

10. Amylin

Amylin is a 37-amino acid peptide secreted from pancreatic β-cells with insulin (Cooper et al., 1987; Westermark et al., 1987). Amylin was originally identified in islet amyloid, the most characteristic feature of T2DM pathology (Opie, 1901). Amylin and insulin are secreted in a molar ratio of 20:1 upon stimulation with glucose (Mitsukawa et al., 1990; Nakazato et al., 1990). Therefore, amylin secretion is reduced in type 1 DM (T1DM). The functional receptors for amylin are complexes of the calcitonin receptor (CTR) and receptor activity-modifying protein (RAMP) 1, 2, or 3. Among these complexes, the CTR/RAMP1 and CTR/RAMP3 complexes are considered the major receptors of amylin based on their binding capacity (Muff, Buhlmann, Fischer, & Born, 1999).

Amylin reduces blood glucose levels by suppressing glucagon secretion (Galderisi et al., 2018). Amylin has been reported to reduce insulin secretion; however, this is controversial (Mather et al., 2002; O'Brien, Westermark, & Johnson, 1990; Ohsawa, Kanatsuka, Yamaguchi, Makino, & Yoshida, 1989). Amylin inhibits food intake and gastric emptying by stimulating the satiety center, and inhibits insulin-induced glucose uptake by isolated myocytes (Westermark, 2011). In T2DM, amyloid, an amylin aggregate, is detected in pancreatic β-cells, and increased amyloid levels lead to cell death (Fernandez, 2014). Amylin is also expressed in the lateral area, arcuate nucleus, and medial preoptic area of the hypothalamus. Although amylin expression was markedly reduced in *ob*/*ob* mice, leptin supplementation restored this reduction. Amylin and leptin caused similar electrophysiological changes in cells expressing leptin receptors in the LHA. After pretreatment with amylin antagonists, no changes were induced by the administration of leptin. Additionally, intraventricular injection of amylin antagonists rapidly reduced the inhibitory effect of leptin on food intake. These findings revealed that the expression of amylin in the hypothalamus is regulated by leptin, and that amylin and leptin act on hypothalamic neurons expressing leptin receptors in a concerted manner to regulate food intake (Li, Kelly, Heiman, Greengard, & Friedman, 2015). Co-administration of amylin and leptin resulted in greater weight loss than administration of amylin alone (Roth et al., 2008). In contrast, when leptin was administered in combination with peptide YY_{3-36} or a GLP-1 receptor agonist, weight loss was comparable to that observed after administration of leptin alone. Pretreatment with amylin before leptin administration partially restored the transduction of leptin signaling (phosphorylated signal transducer and activator of transcription immunoreactivity) in the hypothalamic ventromedial nucleus and hindbrain area postrema (Roth et al., 2008).

The functions of amylin have also been demonstrated in clinical studies. Pramlintide, which lacks amyloidogenicity based on the rat amylin sequence, is used as an injectable drug to treat T1DM and T2DM. Administration of pramlintide to obese patients without DM for 6 weeks significantly reduced body weight (−2.1 kg versus +0.1 kg) and 24 h energy intake (−680 kcal/day versus −191 kcal/day) compared with placebo effects (Smith et al., 2007). In a meta-analysis of double-blind studies on the treatment of T1DM with insulin alone or in combination with pramlintide, body weight, HbA1c level, postprandial blood glucose level, and insulin dose administered were lower in patients receiving combination therapy with insulin and pramlintide (Qiao et al., 2017). Obese subjects without DM were divided into three groups to receive pramlintide, metreleptin, a recombinant human leptin analog, or both. At 20 weeks after treatment, body weight was lower in the combination therapy group than in the other two groups. A significant difference in weight loss started at 4 weeks and continued to increase at 20 weeks (Ravussin et al., 2009) (Table 2). Pramlintide also reduced HbA1c levels by 0.33% and body weight by 2.57 kg compared to placebo in obese T2DM patients (Singh-Franco, Perez, & Harrington, 2011). Pramlintide is administered three times daily because of its short half-life in the blood. An amylin analog with a longer duration of action, cagrilintide, has been developed (Kruse et al., 2021). In a recent clinical study with obese subjects without DM, subjects received a subcutaneous injection of liraglutide 3.0 mg or cagrilintide at 0.3, 0.6, 1.2, 2.4, or 4.5 mg weekly for 26 weeks. Subjects treated with all doses of cagrilintide lost more body weight than placebo, and maximum dose lost more body weight than liraglutide 3.0 mg (Lau et al., 2021) (Table 2).

11. Leptin

Leptin is a 146-amino acid peptide mainly secreted by adipocytes. In humans, plasma leptin concentrations in non-obese subjects, obese subjects, and subjects with leptin gene abnormalities are approximately 20, 100, and 300–700 ng/mL, respectively. The leptin receptor is a class I cytokine receptor family member and has six isoforms in three classes (long, short, and secretory) (Zhou & Rui, 2013). Leptin receptors are expressed in many tissues and cells in the central and peripheral nervous systems (Lee et al., 2002; Papathanassoglou et al., 2006; Seufert, 2004), especially in the arcuate nucleus of the hypothalamus, ventromedial hypothalamus, dorsomedial hypothalamus, PVN, and LHA (Funahashi, Yada, Suzuki, & Shioda, 2003). Leptin receptors are also distributed in peripheral tissues and organs, including islet β-cells, epithelial cells of the intestine, vascular endothelial cells, and the adrenal cortex (Margetic, Gazzola, Pegg, & Hill, 2002). Leptin receptors are single membrane-spanning receptors with multiple isoforms that result from alternative splicing (Lee et al., 1996; Tartaglia et al., 1995). The intracellular domain of leptin receptors binds to Janus kinase 2, a non-receptor protein tyrosine kinase. When leptin binds to the leptin receptor, Janus kinase 2 is activated via autophosphorylation and phosphorylates specific tyrosine residues in the intracellular domain of the leptin receptor (Tartaglia, 1997). Then, transmitters, such as signal transducers and activators of transcription 3, are recruited to these tyrosine residues and activated by phosphorylation of its tyrosine residues. Subsequently, the transmitters are transferred into the nucleus to regulate transcription and transmit signals for the inhibition of food intake and other functions (Bates et al., 2003).

Leptin inhibits food intake by acting on the hypothalamus and promoting energy expenditure by enhancing sympathetic nervous activity, causing weight loss. Leptin also regulates the secretion of pituitary hormones, such as luteinizing hormone, follicle-stimulating hormone, prolactin, and growth hormone. In peripheral tissues, leptin also affects energy homeostasis, insulin action, lipid metabolism, and the immune system (Carlton, Demas, & French, 2012; Dardeno et al., 2010; Moon et al., 2013). Although administration of leptin results in weight loss in normal mice and leptin gene KO *ob*/*ob* mice with marked obesity (Halaas et al., 1995; Pelleymounter et al., 1995), most obese humans have higher blood leptin levels than normal-weight humans, and thus, are leptin-resistant (Horn, Geldszus, Potter, von Zur Muhlen, & Brabant, 1996). There have also been cases of people with mutated leptin genes who exhibited hyperphagia and marked obesity since childhood (Montague et al., 1997).

Lipodystrophy is a congenital or acquired disease characterized by atrophy or the absence of adipose tissue in the entire body or specific areas. Although the causes include specific genes, subcutaneous

Table 2
Clinical trials for amylin analogues

Drugs	Subjects	n	Age	Period	Body weight (kg)		Reference
					Basal	Δ	
Metreleptin	Overweight to obese without T2DM	27	40.5	20 weeks	93.8	−7.4	(Ravussin et al., 2009)
Pramlintide		56	38.3		91.7	−7.9	
Pramlintide + metreleptin		56	38.5		93.9	−11.5 *	
Placebo	Overweight to obese without T2DM	101	51.4	26 weeks	106.2	−3.3	(Lau et al., 2021)
Cagrilintide 0.3 mg		101	53.5		109.8	−6.4 #	
Cagrilintide 0.6 mg		100	53.2		106.2	−7.1 #	
Cagrilintide 1.2 mg		102	52.1		104.4	−9.7 #	
Cagrilintide 2.4 mg		102	52.7		106.8	−10.3 #	
Cagrilintide 4.5 mg		101	51.5		111.0	−11.5 # †	
Liraglutide 3.0 mg		99	51.4		107.8	−9.6 #	

T2DM; type 2 diabetes mellitus
* P<0.05 vs metreleptin
# P<0.05 vs placebo
† P<0.05 vs liraglutide

panniculitis, juvenile rheumatoid arthritis, and human immunodeficiency virus infection, approximately half of the cases are idiopathic (Araujo-Vilar & Santini, 2019). Lipodystrophy is frequently complicated by insulin-resistant DM, hypertriglyceridemia, and fatty liver, among other conditions, and hypoleptinemia is considered responsible for these complications. Metreleptin has been used in Japan since 2013 (Chou & Perry, 2013). Administration of metreleptin to patients with lipodystrophy has been reported to reduce HbA1c levels and improve hypertriglyceridemia, fatty liver disease, and amenorrhea (Araujo-Vilar & Santini, 2019; Oral et al., 2002).

Leptin has been investigated in clinical studies to treat DM and obesity. In a study including eight adult patients with T1DM (BMI: 23.8 ± 1.4) in the United States, metreleptin was subcutaneously injected twice a day for 20 weeks at 0.08 mg/kg/day for men and 0.04 mg/kg/day for women. Although HbA1c levels remained unchanged, body weight decreased by 4.7 kg, and insulin doses were reduced by 15.0% (Vasandani, Clark, Adams-Huet, Quittner, & Garg, 2017). In a double-blind study conducted in the United States, obese patients with T2DM (BMI: 32.7 ± 0.5) were treated with metreleptin (subcutaneously injected at 10 mg twice a day) or placebo for 16 weeks. Although changes in body weight were comparable between the two groups, anti-leptin antibody titers increased over time in the metreleptin group (Moon et al., 2011). In another double-blind study, obese individuals without DM (BMI: 27.5–38.0) received metreleptin (subcutaneously injected at 5 mg twice a day) or a placebo combined with dietetic therapy of −500 kcal/day for 6 months. Body weight decreased in both groups and did not differ (Shetty et al., 2011). When lower abdominal adipose tissue, femoral muscle, and peripheral blood mononuclear cells were used to examine changes after administration of metreleptin to humans, signal transducer and activator of transcription 3, AMP-activated protein kinase, ERK1/2, Akt, mammalian target of rapamycin, nuclear factor-κB, and/or I-κ B kinase α/β were activated.

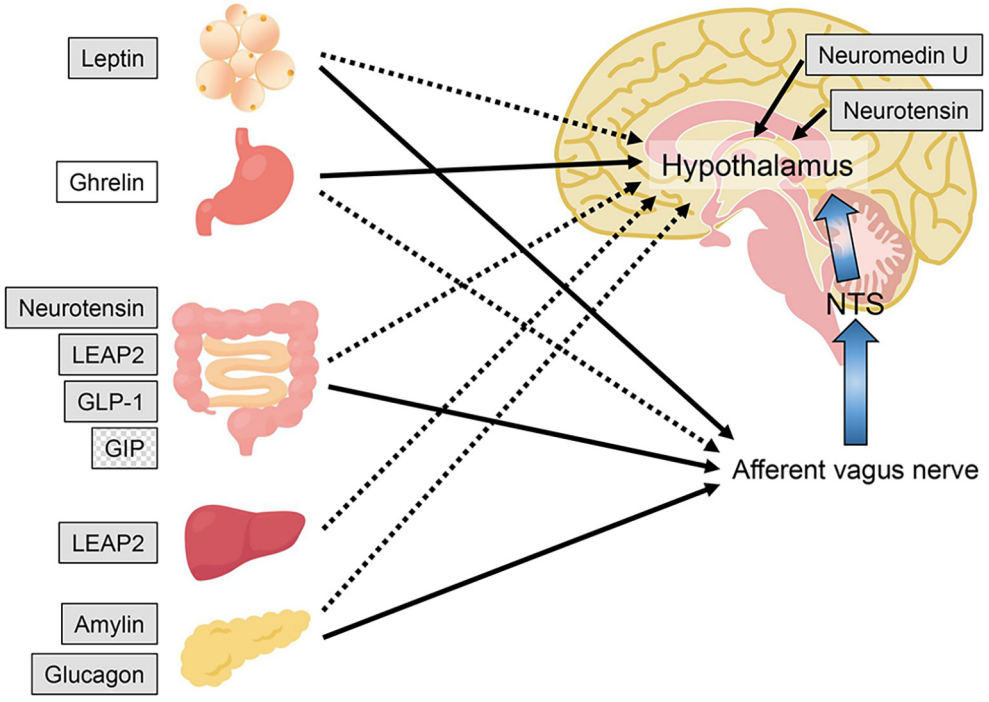

Fig. 5. The gross summary of feeding regulatory effects of eleven peptides. Organs which mainly produce these peptides are shown here. Gray and white inboxes represent anorectic and orexigenic peptides, respectively. The solid and dotted lines indicate stimulatory and inhibitory signals, respectively. Amylin reduces appetite via area postrema and ventral tegmental area, but not the vagus nerve. GIP is in dotted gray inbox because its effects on food intake remain controversial. AgRP, agouti-related protein; NPY, neuropeptide Y; NTS, solitary tract nucleus.

However, no difference in the extent of changes was observed between men and women or between individuals with and without obesity (Moon et al., 2015). Thus, metreleptin monotherapy appears to be less effective for weight loss in obese individuals. However, as mentioned above, metreleptin has been reported to be more effective when used in combination with other drugs.

12. Concluding remarks and future directions

A general overview of eleven substances important for feeding regulation was provided regarding their mechanisms of action, interactions, and clinical application as anti-obesity drugs (Fig. 5). Novel feeding regulatory substances are constantly being identified. Although drugs targeting a single peptide can be expected to reduce body weight to some extent, there are still many unknown factors such as adverse events and long-term effects. In recent years, drugs targeting two or more feeding regulatory substances have been developed to reduce adverse events and increase the potency of weight reduction. New feeding regulatory substances and their receptors continue to be discovered, and their characteristics have yet to be elucidated.

Author's contributions

HU and WZ collected the related literature and wrote the manuscript. MN participated in the design of the review and revised the manuscript. All authors have read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

This study was supported by grants from Suzuken memorial foundation and Japan Foundation for Aging and Health to W. Zhang.

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