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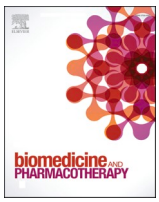

DPP-IV as a potential candidate in anti-obesity and obesity-related diseases treatment

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ABSTRACT

Along with social development and lifestyle changes, the number of overweight and obese patients worldwide is rising annually. Obesity is a chronic metabolic disease with complex etiology. Dipeptidyl peptidase IV (DPP-IV) is a novel adipokine with significantly elevated expression in the visceral fat of obese patients. DPP-IV is a molecule that regulates metabolic homeostasis and inflammatory processes. Through its enzymatic activity, it plays a significant part in achieving hypoglycemic and weight loss effects through various pathways. DPP-IV and DPP-IV inhibitors also have pleiotropic effects in modulating obesity-related diseases by reducing obesity-related inflammation, ameliorating inflammatory bowel disease (IBD), improving hepatic steatosis and lowering cardiovascular risk, and even decreasing the risk of novel coronavirus disease-19 (COVID-19). This paper reviews the mechanisms of action based on DPP-IV targets in obesity and metabolic homeostasis, as well as their active role in the treatment of chronic diseases associated with obesity.

1. Introduction

The latest research report published by The Lancet shows that the global population with obesity reached over 1 billion in 2022. Since 1990, the number of obese adults worldwide has more than doubled, while the number of obese children and adolescents (ages 5–19) has tripled. The data also indicates that in 2022, 43 % of adults were overweight[1]. Obesity is caused by a variety of factors, including the environment (environmental pollution and urbanization), genetics (metabolic rate and fat distribution), neuropsychiatric disorders (psychological stress and exercise psychology), endocrine issues (insulin imbalance and hypothyroidism), abnormal brown adipose tissue (insufficient brown adipose tissue), and others. It is a complex metabolic disorder defined as a body mass index (BMI) $\geq$30 kg/m2[2] (Fig. 1).

Obesity is associated with many chronic diseases such as type II diabetes (T2DM), hypertension, dyslipidemia, cardiovascular disease, inflammatory bowel disease (IBD)[3], non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnea syndrome, higher chance of hospitalization[4,5], and poorer prognosis in patients with coronavirus-19 (COVID-19)[6]. Recent studies[7,8] have shown that obesity is associated with increased cancer risk, recurrence, and poor prognosis. With the global prevalence of overweight and obesity gradually rising, obesity has become one of the greatest global health challenges and a major basis for the development of metabolic diseases.

The novel adipokine known as dipeptidyl peptidase IV (DPP-IV, EC 3.4.14.5), which is secreted by differentiated human adipocytes and strongly expressed in visceral fat of obese patients, is correlated with adipocyte size and markers of metabolic syndrome[9,10]. Glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2), gastric inhibitory polypeptide (GIP), insulin-like growth factor-1 (IGF-1), neuropeptide Y (NPY), and peptide Y (PYY) are among the DPP-IV substrates that have been investigated in vivo. GLP-1 enhances insulin secretion and inhibits glucagon secretion in a glucose-concentration-dependent manner and is capable of delaying gastric emptying[11]. PPY is expressed in the central

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nervous system, decreases appetite, and is also released by enterocytes after food intake along with GLP-1, delaying gastric emptying and reducing intestinal motility and pancreatic exocrine secretion[12]. These mechanisms are related to their roles in diabetes, obesity, and other diseases.

2. Literature search

A narrative literature search was conducted on February 20, 2023. Search terms related to obesity ("obese" OR "obesity" OR "overweight" OR "weight-loss"); DPP-IV ("DPP4" OR "DPP-IV" OR "Dipeptidyl peptidase IV"); obesity treatment ("anti-obesity drugs" OR "bariatric surgery"); obesity-related diseases ("inflammation" OR "hepatic steatosis" OR "cardiovascular disease" OR "COVID-19"); and topics of interest ("etiology" OR "mechanism" OR "comorbidity" OR "structure").

The PubMed database was searched using a combination of these keywords, with results restricted to the years 2013 through 2023 and the language English. The articles were reviewed for relevance based on the title and abstract.

Additional references were identified from the bibliographies of retrieved articles, through additional targeted searches, and through author suggestions.

3. Research status of obesity treatment

Current treatment measures for obesity include lifestyle and behavioral interventions, surgery, and medication. Although lifestyle interventions are recommended, they are difficult to implement in primary care practice and have limited long-term efficacy, mainly due to poor adherence[13,14]. Bariatric surgery (BSG) is frequently preferable to non-surgical therapies for groups that are extremely obese or overweight, but many patients end up with lower-than-expected results because of surgical complications, post-operative malnutrition, and weight gain[15–17]. The research and development of anti-obesity drugs (AOM) have been facing great challenges due to technical and social reasons. There have been a series of AOM that failed after regulatory approval, most of which involved cardiovascular events (sibutramine, fenfluramine, dexfenfluramine, rainbow pills), increased incidence of cancer (lorcaserin), improved risk of suicide (rimonabant), or raised likelihood of drug dependence and abuse (methamphetamine) [18,19]. The U.S. Food and Drug Administration (FDA) approved anti-obesity drugs are orlistat, phentermine, metreleptin, liraglutide, and semaglutide[20,21]. However, the effects of drugs are limited, and many approved drugs have significant side effects. Therefore, the treatment of existing AOM, BSG, or lifestyle management, cannot satisfy the requirements of global medical needs.

4. The structure and function of DPP-IV

DPP-IV, first discovered in 1966[22], is a widely expressed glycoprotein with exopeptidase activity. Its structure was found to be identical to one of the differentiation clusters 26 (CD26), which was then referred to as the activation marker of T lymphocytes, namely the T cell surface antigen CD26[23]. The gene encoding for DPP-IV is located on the long arm of chromosome 2 (2q 24.3), preceded by a promoter region regulated by transcription factors, including the nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB)[24], the hepatocyte nuclear factor 1β (HFN1β)[25], the lysine acetyltransferase 5

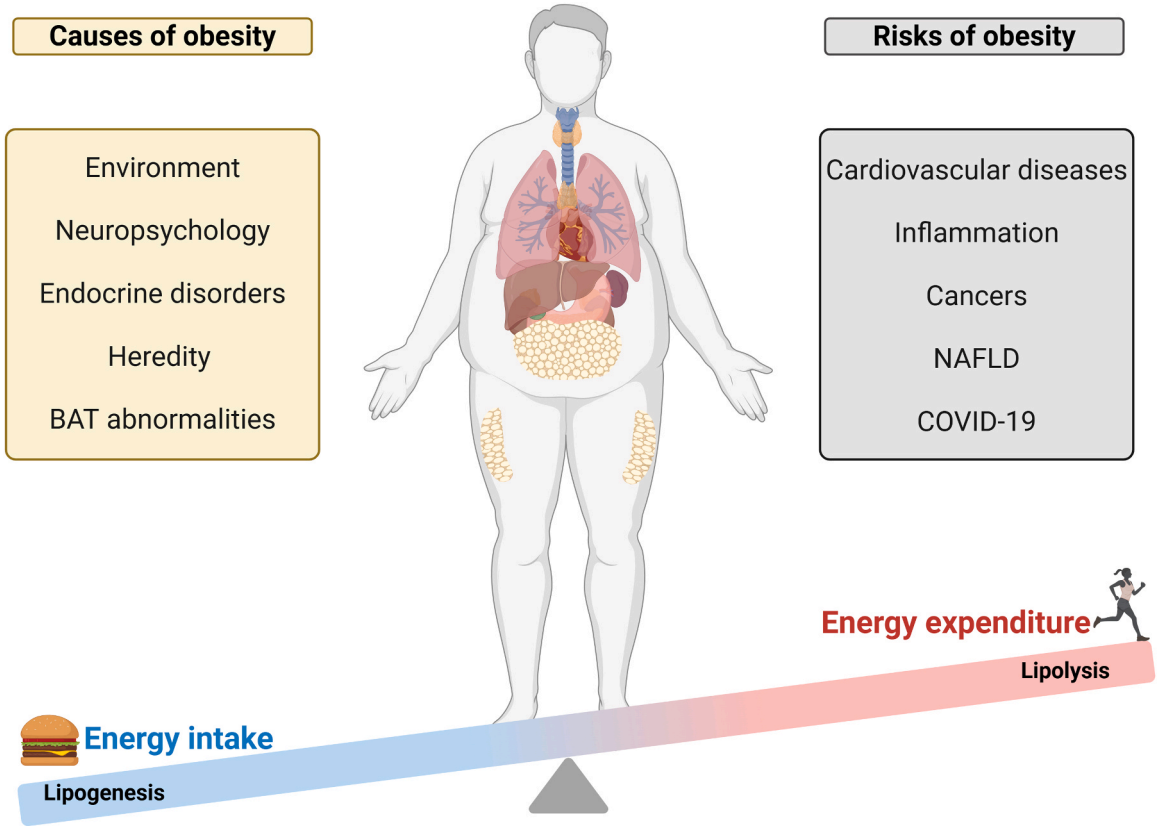

Fig. 1. Factors and Risks Contributing to Obesity. The significant rise in global obesity rates is primarily attributable to increased accessibility to high-energy foods coupled with a reduction in physical activity levels. The etiology of obesity is multifactorial, encompassing environmental influences, neuropsychological factors, endocrine disorders, genetic predispositions, and abnormalities in BAT. The associated risks encompass a wide range of health complications, including cardiovascular disease, chronic inflammation, various malignancies, NAFLD, and heightened susceptibility to COVID-19, BAT-brown adipose tissue. NAFLD- non-alcoholic fatty liver disease. COVID-19- coronavirus-19.

(KAT5)[26], and the signal transducers and activators of transcription 1α (STAT1α)[27], all of which are centrally involved in cell growth and proliferation, immune response and metabolism.

The amino acid sequence of DPP-IV contains the Gly-Trp-Ser-Tyr-Gly motif, which corresponds to the common Gly-X-Ser-X-Gly sequence found in the active sites of many serine proteases. Three critical residues are essential for the enzymatic activity of DPP-IV, namely Gly-629, Ser-631, and Gly-633. Each of the two subunits of DPP-IV consists of two domains: an α/β hydrolase domain and a/β-propeller domain. The catalytic site is located within a large cavity formed between the α/β hydrolase domain and the β-propeller domain. The active site can be accessed through an opening at the center of the β-propeller domain facing the membrane (37=15/22 Å) or through an opening between the hydrolase and propeller domains (20=15/22 Å)[28,29]. DPP-IV exists in two forms, the soluble form (sDPP-IV) and the membrane-bound form. sDPP-IV has enzymatic activity, its main role is to preferentially shear off the first two amino acids from the amino terminus of oligopeptides in which the second amino acid at the amino terminus is alanine or proline[30]. DPP-IV is also a cell surface serine aminopeptidase that is widely expressed on the surfaces of epithelial cells, endothelial cells, stromal cells, stem cells, and immune cells in mice and humans[31]. DPP-IV catabolizes proteins in vivo and has many natural substrates, including growth factors, chemokines, neuropeptides, and vasoactive peptides[32]. Due to the wide range of DPP-IV substrates, impaired sDPP-IV levels and DPP-IV activity have been reported in several metabolic abnormalities such as T2DM, NAFLD, obesity, metabolic syndrome, and polycystic ovary syndrome[33–35]. In addition, elevated levels of DPP-IV have been identified in cancer, autoimmune diseases, and neurodegenerative diseases[36,37]. DPP-IV is involved in a variety of physiological and pathological processes in the body and is associated with the development of many diseases.

5. The role of DPP-IV in metabolism and lipid homeostasis

Several mechanisms or signals[38,39] related to appetite regulation and peripheral energy absorption, storage, and expenditure are gradually being revealed with technological, pharmacological, and surgical developments. Although the mechanisms involved are not yet fully understood, these studies have helped researchers to better understand the development of obesity.

6. Anti-obesity treatment with DPP-IV and GLP-1

6.1. Peripheral signaling pathway

GLP-1 can be secreted by gut enteroendocrine cells and brain preproglucagon (PPG) neurons, defined as the peripheral and central GLP-1 systems, respectively[40]. DPP-IV inhibitors increase GLP-1 levels in vivo by competitively binding to the DPP-IV activation site and decreasing the catalytic activity of the enzyme. Using the protein kinase (PKA)-dependent or guanine nucleotide exchange factor 4 (Epac2) pathway, intestinal-derived GLP-1 activates the glucagon-like peptide-1 receptor (GLP-1R) to increase glucose-stimulated insulin secretion in the periphery[41]. Insulin inhibits lipolysis and fat oxidation while promoting adipogenesis, which results in the accumulation of adipose tissue and ectopic fat storage. Excessive obesity can also result in insulin resistance. Through enhancing PKA activity, lowering endoplasmic reticulum stress, and boosting β-cell function, GLP-1 reduces insulin resistance in obese diabetic mice and promotes weight reduction[42].

PKA improves insulin sensitivity in peripheral tissues by inhibiting adenylate-activated protein kinase (AMPK)-related pathways. AMPK is an important metabolic stress protein kinase that, when activated, enhances skeletal muscle insulin sensitivity by increasing the translocation of glucose transporter protein (GLUT)[43]. Hydroxymethyl glutaryl-CoA (HMG- CoA) and Acetyl-CoA carboxylase (ACC) are key enzymes for cholesterol and fatty acid synthesis, both of which are AMPK substrates[44]. By deactivating their phosphorylation, AMPK can inhibit the accumulation of fat and cholesterol, respectively. AMPK not only acts as an energy receptor at the cellular level, but also participates in regulating energy expenditure and intake, promoting glucolipid metabolism, accelerating fatty acid oxidation, and reducing insulin resistance through hormones and cytokines[45], such as lipocalin and leptin.

PKA also improves insulin sensitivity in peripheral tissues by elevating glyoxalase (GLO)[46]. Healthy adipose tissue is characterized by high vascular density, low hypoxia, fibrosis, and M1 macrophage infiltration. Independent of BMI, it has been demonstrated that restricted adipose tissue capillarization and blood flow are correlated to hypoxia and insulin resistance. As a result, increasing angiogenesis and blood flow may be potential targets for enhancing insulin sensitivity. Down-regulation of adipose tissue expression GLO-1 activity in obese individuals' early stages of metabolic disorders shows that inhibiting it may be a potential strategy for improving the vascular and metabolic function of adipose tissue. In adipocytes, GLP-1-based therapy promotes capillarization, GLO-1 activity, and insulin sensitivity.

Finally, it is also possible to communicate with phosphoinositide 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), and Wnt4/β-catenin, GLP-1 promotes preadipocyte differentiation by upregulating peroxisome proliferator-activated receptor γ (PPARγ) and fatty acid-binding protein 4 (FABP4) and inhibits adipogenesis in mature adipocytes by decreasing fatty acid synthase (FASN) expression[47]. By boosting the expression and activity of the coenzyme I (NAD+) dependent protein deacetylase (Sirt1), the mechanism of which is unclear, GLP-1 also improves white adipose (WAT) lipolysis[48]. Moreover, GLP-1 regulates thermogenesis by inhibiting signaling pathways associated with BMP4 and thereby increasing the production of thermogenic genes including mitochondrial brown lipolytic coupling protein 1 (UCP1)[49]. These mechanism diagrams are shown in Fig. 2.

6.2. Central nervous system signaling pathways

Intestinal-derived GLP-1 activates sensory afferent neurons in the nucleus solitarius through binding to capillaries, the hepatic hila, and nodular ganglion receptors in liver tissue, and through the hypothalamus, activates motor neurons in the vagus nerve, interacting with GLP-1R expressed in the vagus nerve, which transmits information upward through the vagus nerve to the central nervous system (CNS), which in turn inhibits vagal nerve activity and delays gastric emptying, thereby increasing satiety and reducing food intake[50].

Intestinal-derived GLP-1 is involved in the regulation of insulin sensitivity in a CNS-dependent manner[51]. GLP-1 activates vagal sensory neurons projecting to the brainstem in order to initiate efferent vagal reflexes via the parasympathetic branches of the autonomic nervous system. Parasympathetic cells release acetylcholine (ACh) in the islets to activate M-cholinergic receptors and stimulate calcium mobilization in β-cells, and these neurons also release pituitary adenylate cyclase-activating peptide (PACAP), which stimulates β-cell production of cyclic adenosine monophosphate (cAMP), thereby regulating insulin sensitivity.

Intestinal-derived GLP-1 is also implicated in BAT-associated thermogenesis in a CNS-dependent manner, acting through inhibition of the AMPK signaling pathway[52]. AMPK in the ventral medial nucleus of the hypothalamus (VMH) prevents high-fat diet (HFD)-induced obesity by increasing thermogenesis and subsequent energy expenditure in BAT. This effect is dependent on the AMPKα1 isoform in steroidogenic factor 1 (SF1) neurons of VMH, as mice that selectively ablate AMPKα1 in SF1 neurons exhibit resistance to diet-induced obesity, increased thermogenesis of BAT, browning of white adipose tissue, and improved glucose and lipid homeostasis.

Two different kinds of neurons in the arcuate nucleus of the hypothalamus (ARC) control energy metabolism: one type, agouti-related protein (AgRP), which increases appetite; the other,

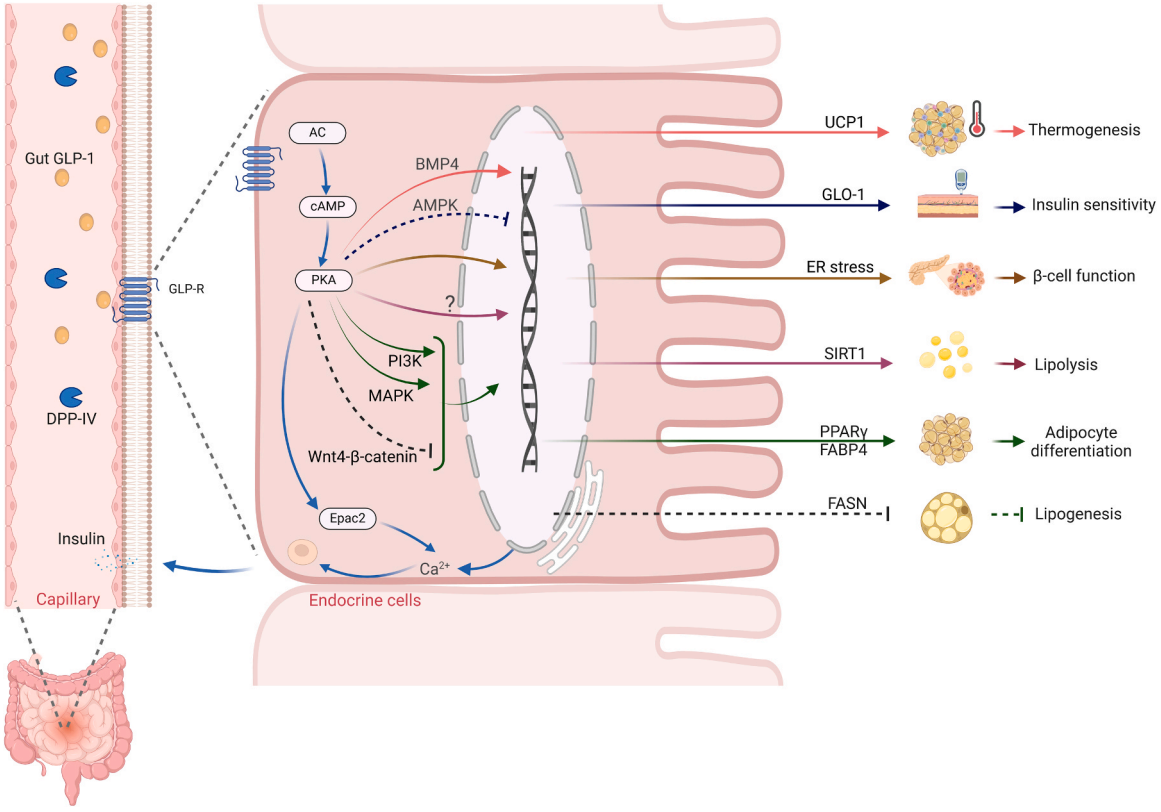

Fig. 2. Peripheral signaling pathway, In the periphery, activation of GLP-R by gut-derived GLP-1 enhances glucose-stimulated insulin secretion via the PKA-dependent or Epac2 pathway. In obese diabetic mice, GLP-1 decreased ER stress, improved β-cell function, and decreased insulin resistance by increasing PKA activity. Also, it increased GLO-1 levels and enhanced insulin sensitivity in peripheral tissues via inhibiting AMPK-related pathways. GLP-1 encourages preadipocyte development by upregulating PPARγ and FABP4 via interacting with several signaling pathways, such as PI3K, MAPK, and Wnt4/β-catenin pathways but inhibits adipogenesis in mature adipocytes by decreasing fatty acid synthase expression. Additionally, GLP-1 enhances lipolysis in WAT by strengthening Sirt1 expression and activity via an unidentified mechanism. Furthermore, by inhibiting the BMP4-related signaling pathway, GLP-1 contributes to the regulation of thermogenesis through raising the expression of thermogenic genes like UCP1, GLP-1- glucagon-like peptide-1. GLP-R- glucagon-like peptide-receptor. PKA- protein kinase A. Epac2- guanine nucleotide exchange factor 4. ER- endoplasmic reticulum. GLO-1- glyoxalase-1. AMPK- adenylate-activated protein kinase. PPARγ- peroxisome proliferator-activated receptor γ. FABP4- fatty acid-binding protein 4. FASN- fatty acid synthase. PI3K- phosphoinositide 3-kinase. MAPK- mitogen-activated protein kinase. WAT- white adipose. BMP4- Bone morphogenetic protein 4. Sirt1- coenzyme I (NAD+) dependent protein deacetylase. UCP1-mitochondrial brown lipolytic coupling protein 1.

proopioidmelanocortin (POMC), which decreases appetite. The hypothalamus receives the central GLP-1 generated by the caudal neurons of the medulla oblongata, which inhibits AgRP/NPY neurons and activates POMC neurons to decrease appetite[53,54]. The activation of AgRP neurons promotes obesity by stimulating appetite and inhibiting energy expenditure, while inhibiting their activity leads to anorexia and weight loss. In contrast, chronic activation of POMC neurons inhibits food intake and increases metabolic rate, and in addition, the absence of functional mutations in the POMC gene leads to overfeeding and obesity in rodents and humans. POMC neurons prevent obesity by releasing alpha-melanocyte-stimulating hormone (α-MSH), which on the one hand suppresses appetite and on the other hand influences the body's energy dissipation by regulating the excitability of the sympathetic nervous system. These mechanism diagrams are shown in Fig. 3.

7. DPP-IV and adipose tissue distribution

Daniela et al.[55] used a proteomic approach to identify DPP-IV as a novel adipokine released by fully differentiated human adipocytes. The amount of DPP-IV secreted considerably increases as adipocytes differentiate. Comparisons with preadipocytes and macrophages indicate that adipocytes from adipose tissue are the primary source of DPP-IV release from intact organs into the circulation.

Research study[9] in both in vitro and in vivo have shown that the expression of DPP-IV in subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) is positively correlated with BMI, and consistently higher than SAT in VAT. DPP-IV was positively correlated with the number of VAT, adipocyte size, and adipose tissue inflammation. DPP-IV inhibitors increase the rate of oxygen consumption in BAT and inguinal white adipose tissue (iWAT) and enhance BAT function by inhibiting extracellular regulated protein kinases (ERKs) signaling pathway activation of β-agonist induced UCP1 expression[56]. DPP-IV inhibitor therapy prevents obesity by activating BAT function.

8. DPP-IV and ectopic fat deposits

Obesity initiates DPP-IV synthesis and secretion by activating the calcium-calmodulin-dependent protein kinase II-transcriptional activator 4 recombinant protein (Ca-CaMKII-ATF4) signaling pathway in mouse hepatocytes[57]. The interleukin 1 receptor-associated kinase 1 recombinant protein-transforming growth factor kinase 1 (IRAK1--TAK1) signaling pathway is activated when sDPP-IV enters adipose tissue through blood circulation and is transported to the core of adipocytes via caveolin-1 (CAV-1). While this is happening, plasma coagulation Factor Xa in the blood activates RAF1 via protease-activated receptor 2 (PAR2), and TAK1 and RAF1 together cause ERK1/2 and NF-κB mediated inflammation, causing macrophage infiltration into visceral adipose tissue and further causing insulin resistance in VAT. It was also found that silencing DPP-IV expression in hepatocytes suppressed VAT inflammation and insulin resistance, which was not seen

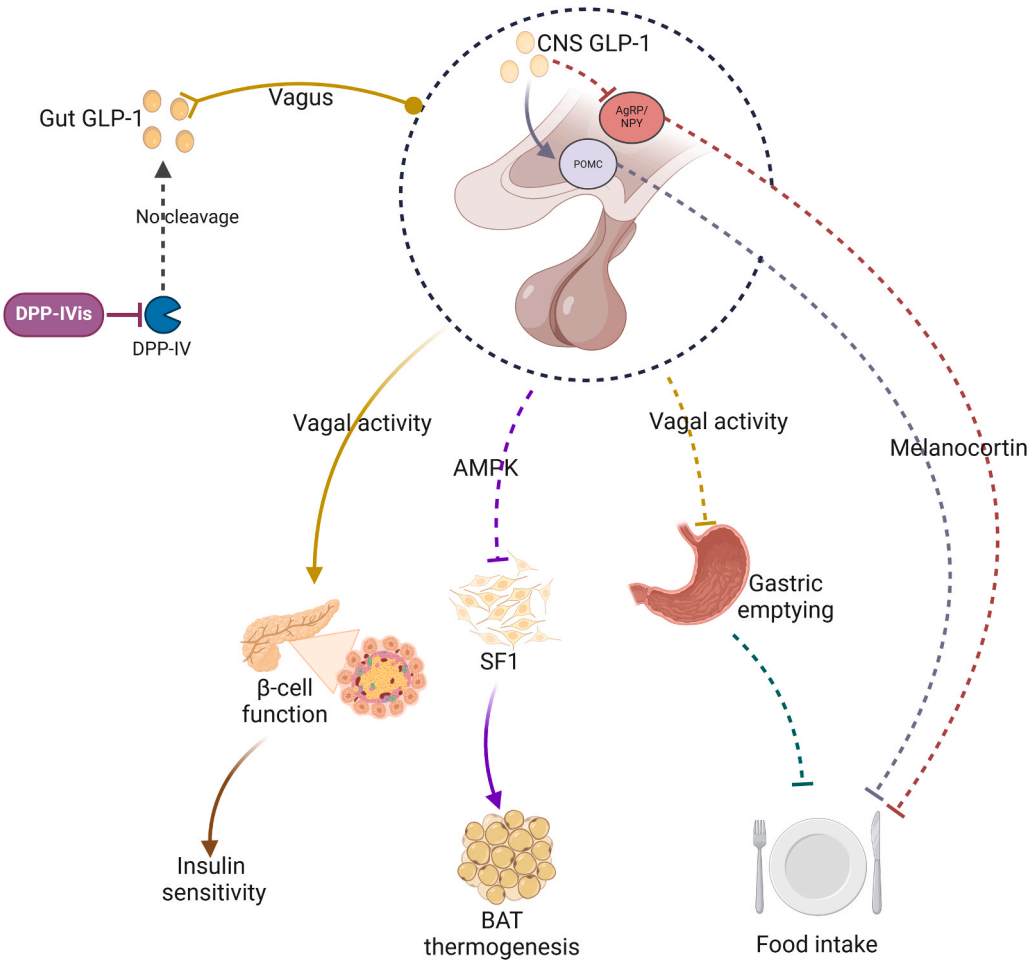

Fig. 3. Central nervous system signaling pathways. Gut-derived GLP-1 and vagus-expressed GLP-R combine to transmit information to the CNS, which in turn reduces vagal activity and stomach emptying to induce satiety and decrease food intake. In addition, gut-derived GLP-1 regulates insulin sensitivity and BAT-related thermogenesis by inhibiting the AMPK signaling pathway in a CNS-dependent manner. GLP-1 activates vagal sensory neurons projecting to the brainstem to initiate efferent vagal reflexes via the parasympathetic branches of the autonomic nervous system, stimulating β-cell production of cAMP and thus regulating insulin sensitivity. By activating POMC neurons while suppressing AgRP/NPY neurons in the hypothalamus, central GLP-1, which is made by neurons in the caudal medulla, reduces food intake. CNS- central nervous system. cAMP- cyclic adenosine monophosphate. PACAP -pituitary adenylate cyclase-activating peptide. VMH -ventral medial nucleus of the hypothalamus. HFD-high-fat diet. SF1-steroidogenic factor 1. ARC-arcuate nucleus of the hypothalamus. AgRP-agouti-related protein. POMC-proopioidmelanocortin. α-MSH-alpha-melanocyte-stimulating hormone.

with oral DPP-IV inhibitors.

sDPP-IV is recommended as a biomarker for NAFLD and has been proven to be a valid indicator of hepatocyte apoptosis and fibrosis[58]. Liver-specific DPP-IV overexpression is associated with higher plasma DPP-IV activity and lower GLP-1 levels. Adiposity and inflammation of adipose tissue increased in response to elevated hepatic DPP-IV activity. Elevated hepatic DPP-IV enhanced peroxisome proliferator-activated receptor-γ (PPARγ) and fatty acid receptor (CD36) expression in the liver. In both people and mice, hepatocyte-specific expression of PPARγ is associated with fatty liver and induces hepatic steatosis. CD36 and monoacylglycerol O-acyltransferase 1 (Mogat1), both of which are associated with fatty liver disease, are the primary targets of PPARγ in the liver.

8.1. DPP-IV and bariatric surgery

BSG is considered a safe and effective alternative therapy for severely obese or overweight individuals with related comorbidities[59]. The mainstream surgical methods are vertical sleeve gastrectomy (VSG) and gastric bypass surgery (RYGB)[60]. A study[61] on glucose metabolism, intestinal hormones, and inflammation after BSG and weight loss medications showed that both groups of patients lost weight. Three months after BSG, there were significant changes in inflammation (decreased fasting hypersensitive C-reactive protein (hs-CRP)), intestinal peptides (decreased fasting GLP-1 levels, increased levels at 30 and 60 minutes postprandial, increased GIP and glucagon levels at 30 minutes postprandial, and increased gastric hunger levels at 60 minutes postprandial), and glucose metabolism (increased glucose and insulin levels at 30 minutes postprandial) concerning hormone levels. BSG did not substantially change plasma DPP-IV activity, and this finding was unrelated to how much weight each group lost.

Other study[62] examined the changes in circulating sDPP-IV during different weight loss interventions and found that sDPP-IV increased with age and weight, was positively associated with insulin resistance and hypertriglyceridemia, but decreased in T2DM. Additionally, it was discovered that after weight reduction surgery and non-surgical interventions over a 6-month period in obese patients with elevated sDPP-IV levels, serum concentrations of sDPP-IV were not changed by weight loss.

Although the BSG is typically preferable to non-surgery, many patients experience less favorable outcomes than anticipated because of postoperative weight regain (WR)[63]. *WR* occurs in about 11∼22 % of patients after BSG[64]. Numerous studies[15] have been conducted on patients who have undergone BSG that demonstrate the utility of AOM

for inadequate weight reduction or weight regain. However, the findings may vary due to the heterogeneity of the study population and the study itself, as well as the fact that these studies primarily involve retrospective analysis and lack prospective analysis.

8.2. DPP-IV and DPP-IV Inhibitors Improve Obesity-Related Diseases

Numerous studies have revealed that DPP-IV and DPP-IV inhibitors regulate obesity-related diseases in multiple effects, including lowering obesity-related inflammation, enhancing liver steatosis, and reducing cardiovascular risk.

8.2.1. Improving obesity-related inflammation

Individuals with obesity cause the hepatocytes to synthesize and secrete DPP-IV because of the accumulation of excess body fat. DPP-IV and plasma Factor-Xa interact to cause adipose tissue macrophage inflammation. Targeted suppression of DPP-IV expression in hepatocytes reduces inflammation and insulin resistance in VAT[57]. Additionally, by controlling the M1/M2 state of macrophages, DPP-IV contributes significantly to the inflammation and insulin resistance brought on by obesity[65]. DPP-IV is primarily produced by M1 macrophages. By causing macrophages in adipose tissue and the liver to polarize to an anti-inflammatory phenotype, DPP-IV antagonists reduce the inflammation and insulin resistance brought on by obesity.

8.2.2. Modulating inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic immune-mediated gastrointestinal disorder, with obesity identified as a significant risk factor associated with its progression[3]. Visceral fat is considered a key contributor to adverse outcomes in patients with IBD. Several prospective studies have evaluated the expression of DPP-IV in small intestine and colon biopsies, as well as surgical specimens from IBD patients and healthy volunteers, demonstrating that DPP-IV may serve as a biomarker for treatment escalation and response to biologic therapy in IBD patients [3,66]. Vilda is a potent DPP-IV inhibitor that has shown promising colonic protective and anti-ulcer properties in studies involving albino rats, effectively countering oxidant-induced ulcerative colitis (UC)[67]. This effect is achieved through the reduction of colonic inflammation, alleviation of oxidative and endoplasmic reticulum stress, improvement of mitochondrial function, and promotion of colonic autophagy via the modulation of the PI3K/AKT/mTOR and AMPK/Nrf2 signaling pathways. These findings suggest that Vilda may represent a promising therapeutic option for UC.

8.2.3. Improving hepatic steatosis

NAFLD has become a metabolic liver disease that affects about a quarter of the world's population[68]. Obesity is an independent risk factor for NAFLD[69]. The degree of obesity and fat distribution affect the prevalence of NAFLD. In animal studies[34,70], increased levels of hepatic DPP-IV expression promote the development of NAFLD. Several studies[71,72] also have reported the therapeutic potential of DPP-IV inhibitors for the treatment of non-alcoholic steatohepatitis (NASH) in animals and humans. DPP-IV inhibitors ameliorate the pathogenesis of NASH, inhibit adipose apoptosis, and downregulate hepatic DPP-IV expression. In addition, pro-inflammatory and pro-fibrogenic factors are reduced by DPP-IV inhibitors both in vivo and in vitro, indicating that DPP-IV inhibitors alter the progression of NASH. Furthermore[73], hematopoietic stem cell modulation can also contribute to the protective effect of DPP-IV inhibitors against NASH. Another study[74] has reported that DPP-IV inhibitors have been proven to induce autophagy, which is generally considered to prevent fatty liver, degrade damaged cell components in liver cells, and improve liver steatosis.

8.2.4. Reducing the risk of cardiovascular disease

Being overweight causes the accumulation of visceral fat. Compression of the viscera and blood arteries will result in an increase in blood pressure, cholesterol, triglycerides, and low-density lipoprotein (LDL) levels. Chronic hypertension and hyperlipidemia are risk factors for atherosclerosis, coronary heart disease, and stroke. DPP-IV was found to be widely expressed in the vascular system, including endothelial cells, macrophages, cardiomyocytes, smooth muscle cells, valvular interstitial cells, and other cell types, suggesting its possible involvement in the development and progression of cardiovascular disease[75]. Five large-scale clinical trials[76–80] have been completed to demonstrate the cardiovascular safety of DPP-IV inhibitors. More and more studies [81–83] have found that DPP-IV inhibitors also have protective effects on a variety of cardiovascular diseases, such as hyperlipidemia, hypertension, aortic valve calcification, coronary atherosclerosis, and heart failure. A randomized placebo-controlled mechanistic study known as the "Vildagliptin in Ventricular Dysfunction Diabetes Trial" (VIVIDD) demonstrated that the DPP-IV inhibitor vildagliptin significantly improved outcomes in 254 patients with T2DM, heart failure, and systolic dysfunction when used in conjunction with standard glycemic and heart failure therapies[84]. In another study[85], researchers from the UK, Greece, and Germany identified a method for treating insulin-induced vascular injury associated with heart disease. They utilized DPP-IV inhibitors to treat both mice and human patients, successfully reducing oxidative stress responses in the vasculature and reversing vascular damage caused by a high-fat diet in both humans and mice. Wang et al.[86] found that DUSP26 contributes to the treatment of calcific aortic valve disease (CAVD) by inhibiting DPP-IV ubiquitination and degradation induced by Mouse Double Minute 2 (MDM2) in human valvular interstitial cells (hVICs). Katia et al.[87] discovered that the DPP-IV inhibitor sitagliptin stimulates resident cardiac stem cells and promotes neovascularization in patients with diabetic cardiomyopathy, reducing cardiac remodeling, improving myocardial function, and enhancing survival rates following myocardial infarction.

8.3. DPP-IV and DPP-IV Inhibitors Reduce the Risk of COVID-19

Patients with chronic underlying diseases are more likely to be infected with COVID-19 during the recent worldwide pandemic of COVID-19. According to studies[88,89], being overweight and obese may also be risk factors for COVID-19. COVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2). sDPP-IV can bind SARS-CoV-2 and prevent the virus from attaching to membrane-bound DPP-IV in host cells, thus preventing virus transmission. A German study[90] shows reduced circulating levels of sDPP-IV in patients with severe neo-coronary pneumonia. Naveen et al. [91] predicted the molecular model of SARS-CoV-2, they found that the S1 domain of spike glycoprotein of SARS-CoV-2 may directly interact with DPP-IV in host cells, indicating that DPP-IV may be a common receptor for SARS-CoV-2 virus entry. In various clinical chronic diseases such as diabetes, obesity, and metabolic syndrome, serum sDPP-IV levels are also changed and related to insulin resistance[92]. These studies may also contribute to greater susceptibility to SARS-CoV-2 infection in diabetes, obesity, and the elderly. By raising sDPP-IV levels to improve the sequestration of viral particles in circulation, DPP-IV inhibitors can prevent viral entry into the body and reduce viral growth in humans [93]. The immunomodulatory effect of DPP-IV inhibitor can prevent cytokine storms in patients with COVID-19, thereby reducing the severity of the disease[94]. The importance of DPP-IV and DPP-IV inhibitors in COVID-19 has gradually been recognized.

9. Conclusion

In 1948[95], obesity was first included in the International Classification of Diseases, but did not attract much attention. In 1997, the World Health Organization (WHO) listed obesity as a chronic disease. In 2013[96], the American Medical Association passed a motion describing obesity as a "disease state with multiple pathophysiological aspects". In 2021[97], the European Commission issued a brief defining obesity as "a

chronic recurrent disease and thus a gateway to a range of other non-communicable diseases". These fully emphasize that obesity is not only a risk factor for various diseases but that obesity itself is an independent chronic disease. At present, the global prevalence of obesity continues to increase. WHO[98] estimates that by 2025, one in five adults worldwide will have obesity.

One environmental factor contributing to the rapid rise in obesity worldwide is increased access to high-energy foods and a decline in physical activity (Fig. 1). Antiepileptic and psychotropic drugs affect the regulation of appetite by the central nervous system. Chronic stress, sleep deprivation, and misaligned circadian cycles can all cause the body's endocrine system to become dysregulated. These factors may also contribute to obesity. The emergence of simple obesity in people also has a genetic basis. Obesity is a metabolic disease associated with multiple factors.

The management of AOM has a long history, full of hopes and disappointments. Comorbid conditions and the increased risk of vascular disease in obese individuals make it more difficult to evaluate the safety of AOM. Furthermore, it is very challenging to carry out extensive, long-term clinical studies on individuals who have heterologous obesity. Through its enzyme activity, the molecule DPP-IV is crucial in controlling metabolic balance and inflammatory responses. Targeting DPP-IV, it treats obesity by enhancing the activity of the substrate GLP-1, stimulating insulin release, delaying gastric emptying, and increasing satiety, among other mechanisms. In addition, by improving adipose tissue inflammation, promoting adipose tissue remodeling, and reducing ectopic adipose tissue deposition, it also regulates adipose tissue's function in metabolism and lipid homeostasis. Since BSG results in altered gastrointestinal hormone secretion, but not circulating DPP-IV levels, the possibility of combining treatment targeting DPP-IV after bariatric surgery to enhance the anti-obesity effect requires long-term, large-scale, multicenter clinical studies to evaluate its safety and efficacy. The mechanisms of action based on DPP-IV targets in obesity and metabolic balance are reviewed in this study, as well as their practical application in the management of chronic disorders linked to obesity.

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Author contributions

All the authors participated in writing the manuscript and in drawing the figures. All authors read and approved the final manuscript.

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Huolun Feng: Writing – review & editing, Validation, Supervision, Methodology, Investigation. **Jiabin Zheng:** Writing – review & editing, Validation, Supervision, Project administration. **Liyang Cai:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation. **Yong Li:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis. **Xin Guo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation.

Declaration of Competing Interest

The authors declare no competing interests.

Data availability

No data was used for the research described in the article.

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