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REVIEW

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Adipokines in glucose and lipid metabolism

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ABSTRACT
Adipokines are proteins secreted by adipose tissue to regulate glucolipid metabolism and play vital roles in our body. Different adipokines have more than one endocrine function and be divided into several different categories according to their functions, including adipokines involved in glucolipid metabolism, the inflammatory response, insulin action, activation of brown adipose tissue (BAT) and appetite regulation. Multiple adipokines interact with each other to regulate metabolic processes. Based on the recent progress of adipokine research, this article discusses the role and mechanism of various adipokines in glucolipid metabolism, which may provide new ideas for understanding the pathogenesis and improving the treatment of various metabolic diseases.

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Introduction

In 1987, Bruce Spiegelman, a professor at the Dana-Farber Cancer Institute and Harvard Medical School, first discovered the adipokine adipsin [1]. By 1994, the discovery of leptin further changed the traditional view of adipose tissue as an energy storage organ for many years and opened a new era in human research on adipose tissue. In the past several decades, with the societal development, the morbidity rate of obesity has increased, arousing global health concerns including insulin resistance, type 2 diabetes, and metabolic – associated fatty liver disease (MAFLD). With an increasing number of studies focusing on adipose tissue, it is now clear that adipose tissue has a complex and active metabolic endocrine function, that secretes a variety of adipokines, such as leptin and adiponectin, which act locally in adipose tissue (paracrine or autocrine) or via blood circulation to distant target organs. The abnormal secretion or action of these adipokines directly or indirectly leads to metabolic disorders, such as obesity, diabetes, hyperlipidaemia, and other metabolic syndromes. At present, although the understanding of adipokines has improved, there are still vast unknowns that need to be further explored. To better understand the role of adipose tissue and the effects of different adipokines on glucolipid metabolism, this paper presents a systematic review of the more studied adipokines in recent years, with the aim of providing an overview of the relevant studies in this field and suggesting possible research directions in the diagnosis and treatment of metabolic syndrome diseases.

Effects of adipokines on glucose metabolism

Glucose enters cells in various ways, including passive diffusion, facilitated diffusion and active transport, with glut4-mediated facilitated diffusion being the main mode in muscle and adipocytes. Glucose utilization occurs mainly through glycolysis, aerobic oxidation, and glycogen synthesis. Multiple adipokines are involved in the process of glucose metabolism and exert different functions. Adipsin, adiponectin, C1q/TNF-related proteins (CTRPs), fibroblast growth factor-21 (FGF21), leptin, and insulin-like growth factor binding protein-2 (IGFBP2) promote glucose metabolism and lower blood glucose levels. In contrast, resistin has a blood glucose-raising effect.

Adipsin, the first described adipokine, is a member of the serine protease family found in 3T3 adipocytes. Later studies found that adipsin was identified as complement factor D, which participates in an alternative pathway of the complement system [2]. A study showed that long-term chronic supplementation of adipsin in db/db mice ameliorates hyperglycaemia and increases insulin levels while preserving beta cells by blocking dedifferentiation and death [3]. Type 2 diabetes mellitus (T2DM) patients with β cell failure are deficient in adipsin. Adipsin catalyses the release of complement factor C3a, which has been shown to stimulate insulin production in pancreatic β cells [4]. A clinical study of the relationship between serum adipsin and the first phase of glucose-stimulated insulin secretion in individuals with different glucose

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tolerances showed that serum adipsin levels were lower in patients with T2DM and impaired glucose tolerance (IGT) and were positively correlated with the first phase of insulin secretion [5]. Furthermore, adipsin facilitates glucose uptake, increases triglyceride synthesis in adipocytes and inhibits lipolysis [6]. Taken together, these recent findings suggest that adipsin plays an important role in maintaining the homoeostasis of adipose tissue and pancreatic β cell function.

Adiponectin is a secreted protein encoded by the *apM1* gene. The biological function of adiponectin is mainly mediated by adiponectin receptor 1 and adiponectin receptor 2(AdipoR1/R2), which have seven transmembrane domains, with their N-terminus inside the cell and the C-terminus facing outwards. This topology is opposite to all-known G-protein coupled receptors [7]. In addition to AdipoR1/R2, T-cadherin is another receptor that is highly expressed in the cardiovascular system. Adiponectin/T-cadherin plays a role in reducing atherosclerosis and protecting the cardiovascular system, and mammalian cell-based studies have suggested that T-cadherin is the major binding partner of native adiponectin in serum [8,9]. Decreased adiponectin and receptor levels are present in adults with obesity and T2DM [10].

There is a highly conserved 13-residue fragment, ADP-1, in the collagen structural domain of adiponectin. ADP-1 activates AMP-activated protein kinase (AMPK) and p38 mitogen-activated protein kinase (MAPK) in an adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1 (APPL1)-dependent pathway and stimulates basal glucose transporter type 4 (GLUT4) translocation and glucose uptake in rat skeletal muscle cells (L6 myotubes) [11,12]. In hippocampal neurons, adiponectin enhances glucose uptake, glycolytic rate, and ATP production in an AMPK-dependent manner [13]. Adiponectin stimulates the interaction between APPL1 and Rab5 (a small GTPase), leading to increased GLUT4 membrane translocation [14]. Rab5 plays a pivotal role in APPL1-mediated adiponectin signalling, and impaired GTPase Rab5 expression has been found in adipocytes in patients with obesity and T2DM [15,16] (Figure 1). Adiponectin is a kind of globular protein and has a similar structure to CTRPs. Specially, CTRP9 shows the highest degree of amino acid identity to adiponectin in its globular C1q domain (approximately 51%). The function of CTRP9 is to promote glucose metabolism, similar to adiponectin [17,18]. In contrast to the function of adiponectin, resistin inhibits glucose metabolism by inhibiting hexokinase activity and reducing glucose uptake into adipocytes, muscle cells and other tissues [13].

FGF21 is a metabolic hormone synthesized by various tissues; when secreted by adipose tissue it is called adipokine, by the liver it is called hepatokine, and by muscle it is called myokine. It was recently recognized as a metabolic regulator that exerts paracrine and endocrine control of many aspects of energy homoeostasis in multiple tissues. In the above, we described the role of adiponectin in glucose metabolism. Treatments with FGF21 enhanced both the expression and secretion of adiponectin in adipocytes, thereby increasing serum levels of adiponectin in mice [19]. This shows that FGF21, as an adipokine, regulates glucose homoeostasis and insulin sensitivity through adiponectin mediation

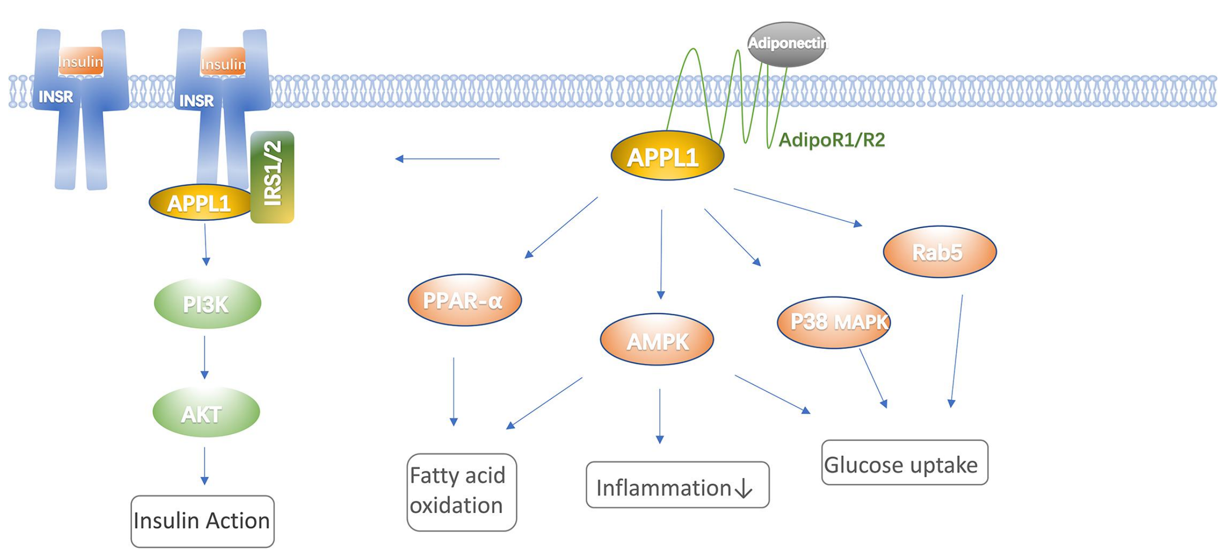

Figure 1. Adiponectin and insulin signalling. APPL1 interacts with AdipoR1 or AdipoR2 and mediates the activation of multiple pathways including PPAR-α, AMPK and p38 MAPK by adiponectin, then triggers a cascade of biological responses. Most of the metabolic effects of insulin are mediated by PI3K/AKT pathway. APPL1 enhances crosstalk between the insulin and adiponectin signalling pathways, by promoting the interaction of IRS1/2 and insulin receptor.

[19,20]. However, a 2017 study suggested that adiponectin is dispensable for the chronic effects of FGF21 on energy expenditure and insulin sensitivity [21]. FGF21 predominantly binds to the receptor FGFR1c, and this process requires the cofactor β-Klotho (KLB) to achieve ligand-receptor interactions [22]. Then, tyrosine kinase activity is initiated which further activates the MAPK pathway. MAPK activates extracellular signal-related kinase (ERK) 1 and ERK2, which enter the nucleus and stimulate the transcription of target genes [23,24]. In mice, selective ablation of β- klotho in adipocytes attenuates the acute but not chronic effects of FGF21 administration on glucose uptake and insulin sensitivity, suggesting that FGF21 exerts its metabolic actions through both adipose- dependent and adipose- independent mechanisms. Furthermore, this study also explored whether this effect was mediated through brown adipocytes [21]. In human adipose tissue, FGF21 also plays an important role in white adipose tissue (WAT) browning, brown adipocyte activation and lipolysis, as we will describe in the following sections.

Most FGF21 in the blood is secreted by the liver. FGF21 hepatokine responds to glucose response. In humans and mice, fructose induction increases FGF21 levels, and carbohydrate-responsive element-binding protein (CHREBP) is involved in this process. CHREBP deletion may blunt hepatic FGF21 transcription and secretion in response to glucose [25–28]. Single nucleotide polymorphisms (SNPs) in the FGF21 gene are associated with increased sweet taste preference [29]. Studies in rats, monkeys, and humans have shown that FGF21 moderates simple sugar intake and preferences for sweet foods by signalling with FGF21 receptors in the paraventricular nucleus of the hypothalamus [30,31]. The mechanism of FGF21 action and the tissues responsible for these actions have been controversial, but the important role of FGF21 in metabolism is clear.

Regulation of glucose metabolism by leptin is mediated both centrally and via peripheral tissues and is influenced by the activation status of insulin signalling pathways. The central nervous system (CNS)is currently considered the primary site of leptin activity. Leptin receptors (LEPRs) are expressed primarily in gamma-aminobutyric acid (GABA) neurons in the hypothalamus. Additionally, in other regions of the hypothalamus, including the ventral medial hypothalamic nucleus (VMH) and the arcuate nucleus of the hypothalamus (ARC), the expression levels are low [32,33]. Perry et al. found that leptin deficiency activated the hypothalamic-pituitary-adrenal (HPA) axis, causing elevated blood glucose and even diabetic ketoacidosis (DKA). Leptin acutely suppresses lipolysis and hepatic glucose production(HGP) and reverses DKA in an insulin-independent manner by suppressing the HPA axis [34]. In addition, leptin is involved in glucose sensing in the hypothalamus. In short-term high-fat fed or uncontrolled diabetic mice, hypothalamic leptin infusion was found to enhance hypothalamic glucose sensing and restore glucose homoeostasis. It activates PI3K and/or STAT3 and enhances lactate metabolism to regulate glucose homoeostasis, but the underlying mechanisms require future investigation [35]. For the peripheral tissues, leptin inhibits hepatic gluconeogenesis, increases insulin sensitivity in the liver and promotes glucose uptake and utilization in skeletal and cardiac muscle [36–38]. Leptin can also mediate a glucose-fatty acid cycle to maintain glucose homoeostasis in starvation. In 48-hr fasted rats, physiologic leptin replacement suppresses lipolysis and reduces plasma glucose, but supraphysiologic leptin stimulates lipolysis and increases plasma glucose [39]. In addition, leptin is involved in the regulation of insulin-regulated intercellular signalling pathways. Leptin deficiency affects glucose homoeostasis [40]. In addition, it plays an important role in the regulation of appetite, as we will elaborate in the following sections.

The regulation of blood glucose by leptin can also be mediated by IGFBP [41]. IGFBP2 is a binding protein synthesized during adipogenesis that has been demonstrated to promote glucose uptake by myotubular cells [42]. However, the mechanism of IGFBP2 action still needs further investigation.

Adipokines in lipid metabolism

Fatty acid oxidation is an important source of energy in the body and is most active in the liver and muscle. Many adipokines such as FGF21, adiponectin, FABP4, IGFBP2 and CTRPs, are involved in this process, regulating lipid metabolism and energy production and consumption.

Peroxisome proliferator-activated receptor (PPAR) α is a nuclear receptor activated by fatty acids and is required for the normal adaptive response to starvation. PPARα is highly expressed in tissues associated with fatty acid oxidation (e.g. liver and skeletal muscle), and its activation reduces plasma triglyceride (TG) and increases high-density lipoprotein (HDL) levels [26,43]. Mice lacking PPARα accumulate hepatic triglycerides and become hypoketonemic during fasting and starvation [44,45]. Drugs targeting this mechanism have been used in the clinic. For example, the lipid-lowering drug fibrates are PPAR-α activators, and the glucose-lowering drug thiazolidinediones are PPAR-γ agonists [43,46]. Adiponectin greatly increases the expression and activity of PPAR-α and upregulates acetyl coenzyme A oxidase and uncoupling protein (UCP), thereby promoting fatty acid oxidation and energy expenditure [11,47]. In a clinical study, it was found that HDL-C was independently correlated with adiponectin in nondiabetic men and women [48]. The mechanism may be that adiponectin enhances the secretion of apolipoprotein A-I (apo-AI), which is the major apolipoprotein of HDL, and the expression of ATP-binding cassette transporter A1 (A-BCA1), which induces HDL assembly through reverse cholesterol transport in hepatic cells [49,50]. In addition, many previous studies have demonstrated that circulating adiponectin is negatively correlated with TG and very low-density lipoprotein (VLDL) [51,52]. A possible explanation is the regulation of lipoprotein lipase (LPL) activity by adiponectin, resulting in increased TG catabolism [47]. As mentioned earlier, the adipokine FGF21 induces adiponectin; thus, it plays a similar role to adiponectin. FGF21, as a hepatokine also plays an important role in FFA transport and lipolysis, which will not be discussed here [53].

Fatty acid transport requires the involvement of fatty acid-binding protein 4(FABP4), a class of intracellular lipid chaperone proteins that are abundantly expressed in macrophages and adipocytes. FABP4 maintains adipocyte homoeostasis and regulates lipolysis and lipogenesis by interacting with hormone-sensitive lipases (HSL) and PPAR-γ [54]. Dou et al. reported that exogenous injection of FABP4 into mice significantly reduced intracellular triglyceride content; decreased the expression of the lipogenic markers PPAR-γ, CCAAT/enhancer binding protein α(C/EBPα), intracellular FABP4 and adiponectin; interfered with adipocyte differentiation; promoted lipolysis in adipocytes involved in p38 MAPK and induced adipocyte inflammation in 3T3-L1 cells [55,56]. In addition, FABP4 plays a very important role in the regulation of energy storage and glucose homoeostasis [54,57].

The CTRP family is a superfamily of aliphatic factors secreted mainly by adipose tissue with similar structural characteristics. Its biological functions are mainly related to anti-inflammation, metabolism, and immunity. Some CTRP subtypes enhance fatty acid oxidation in muscle cells and regulate lipid metabolism. CTRP6 plays an essential regulatory role in fat development, promoting the expression of adipogenic genes, reducing the expression of lipolytic genes and decreasing the activation of p38MAPK. Knockdown of CTRP6 reduces the deposition of fat in pigs [58,59]. Another subtype, CTRP3, negatively regulates lipid metabolism during adipocyte differentiation. It has been reported that CTRP3-treated rats have reduced hepatic fatty acid synthesis and attenuated hepatic steatosis, but the mechanism is not clear [60]. Among young children (aged 7–10 years) total CTRP3 concentration was positively correlated with HDL but negatively correlated with TG and VLDL [61]. In women with gestational diabetes mellitus (GDM), fasting serum CTRP3 was positively correlated with HDL-C and HOMA-β, which may reveal the protective role of CTRP3 in the development of GDM [62,63].

In addition, IGFBP-2 can inhibit human visceral adipogenesis and lipogenesis and may have a limiting role on excess visceral fat, but not subcutaneous adipocytes [64,65]. In a population-based cross-sectional study, IGFBP2 was negatively associated with VLDL and TG levels but not with HDL [66]. After one year of lifestyle and diet changes, elevated IGFBP2 levels were strongly associated with lower low-density lipoprotein (LDL) and apo B (the major apolipoprotein of LDL) concentrations [67]. Stable isotope-labelled leucine-based tracers for lipoprotein kinetic assays suggest that the negative correlation between plasma IGFBP-2 levels and TG concentrations may be due to impaired clearance of VLDL and IDL particles by apo B −100 and increased production of coeliac particles by apo B −48, but additional studies are necessary to investigate the mechanisms [68].

Insulin resistance

The insulin signalling pathway is triggered by the binding of insulin to transmembrane insulin receptors (INSRs), followed by the activation of insulin receptor substrates (IRSs) and the downstream PI3K-AKT signalling pathway (Figure 1), resulting in increased protein synthesis, lipogenesis, glucose uptake and utilization, glycogen synthesis, and reduced lipolysis and gluconeogenesis [69]. Many factors can inhibit this pathway and lead to insulin resistance, such as chronic inflammation, cellular nutrient stress, and lipid factors [70,71].

Multiple adipokines have been reported to be involved in insulin resistance. Retinol binding protein 4 (RBP4) is a member of the lipocalin family and the major transport protein of retinol. RBP4 is the most highly expressed adipokine in liver, followed by adipose tissue [72,73], and it is elevated in the serum of people with obesity and/or T2DM [74,75]. In experiments with mice, RBP4 activates both CD4-positive T cells and macrophages through Toll-like receptor 4 (TLR4, major receptor mediating the endotoxin-induced inflammatory response)- and c-Jun N-terminal kinase (JNK)-dependent pathways, resulting in the upregulation of proinflammatory cytokines [76,77]. These inflammatory factors increase lipolysis and promote insulin resistance

[78]. However, finding in the clinic have been inconsistent as several clinical studies have found that insulin resistance is not associated with circulating levels of RBP4 [79–81].

Fetuin-A (FetA) is a glycoprotein that is secreted by the liver and adipose tissue [82,83]. It activates macrophages to induce inflammation and causes insulin resistance. Blocking certain inflammatory signalling pathways can protect mice from FetA-mediated insulin resistance and partially restore insulin secretion [84–86]. As the function of FetA is gradually clarified, it is considered a potential biological indicator of insulin resistance [87,88].

There is broad consensus that adiponectin is an anti-insulin resistance adipokine. As previously described, APPL1 interacts with adiponectin receptors and multiple pathways [12,16]. APPL1 forms a complex with IRS1/2, and this complex is then recruited to INSR and enhances insulin signal transduction. High-fat diet and obese mice have reduced adiponectin levels and AdipoR2 expression, impairing adiponectin signalling and causing insulin resistance [89,90]. In addition, a high level of resistin is positively associated with insulin resistance in obese and T2DM patients [91], which does not exist in healthy people [91,92]. Resistin induces an inflammatory response through the TLR4 signalling pathway, leading to insulin resistance [93,94].

Since IGFBP-2 is structurally similar to insulin, it is associated with insulin resistance and negatively correlated with weight and metabolic dysfunction indicators. Serum IGFBP-2 levels were significantly lower in overweight or obese children than in controls and circulating IGFBP-2 levels in overweight or obese children were positively correlated with insulin sensitivity [95,96]. These results suggested that IGFBP-2 might be a promising marker for the early recognition of insulin resistance, especially in overweight or obese children [95–97]. Many other adipokines are closely related to insulin resistance, which is negatively correlated with FGF21, leptin and omentin-1 concentrations [98–100] and positively correlated with CTRP9 and vaspin [101,102]. Although an increasing number of biomarkers have been developed for the prediction of insulin sensitivity [103], their accuracy and efficacy are still un satisfactory for the early detection and treatment of insulin resistance.

Function of adipokines during white fat conversion into brown

It has long been thought that there are two different adipocytes in mammals – white and brown adipocytes, whereas white adipocytes contain large unilocular lipid droplets and few mitochondria, and their main function is to store energy. Brown adipocytes contain multilocular lipid droplets and many mitochondria expressing UCP1, which converts energy into heat. While recent studies have demonstrated the existence of UCP1-independent thermogenic pathways [104], UCP1 is still the main regulator of thermogenesis in BAT, as numerous studies have revealed. In recent years, a new type of adipose adipocyte has been discovered, beige adipocytes [105]. In response to stimulation by cold, catecholamines, exercise, and thiazolidinediones (TZDs), white adipocytes turn brown and produce heat-producing adipocytes, also known as beige adipocytes. Beige adipocytes are intermediates in the transformation of white adipocytes to brown adipocytes, and their morphology and function are similar to those of brown adipocytes [106,107] (Figure 2).

Glycogen is a major mechanism of energy storage and utilization [108]. A research team found that glycogen (PTG) -knockout (KO) mice have reduced UCP1 expression and energy expenditure [109]. In addition, the expression of glycogen metabolism genes in adipose tissue was negatively associated with obesity in two independent populations [109]. Glycogen metabolism links glucose homoeostasis to thermogenesis in adipocytes, which provides a new concept of white fat conversion into brown fat.

White adipocytes produce large amounts of adipokines including leptin, adiponectin, omentin, FABP4 and inflammatory factors. The effect of adipokines secreted by WAT on glycolipid metabolism has been described in other chapters.

Brown and beige adipose tissues are known principally for their thermogenic effects. However, in recent years, it has been discovered that, similar to WAT, brown and beige adipose tissues also play an important role in the regulation of metabolic health through the secretion of various adipokines, called batokines, including vascular endothelial growth factor A (VEGFA), chemokine C-X-C motif chemokine ligand-14 (CXCL14), FGF21, bone morphogenetic proteins (BMPs), interleukin(IL)-6, and neuregulin 4 (NRG4) [110–112]. These adipokines, which act in a paracrine or autocrine manner, play a vital role in glucolipid metabolism and the transformation of adipose tissue types. For example, BAT-mediated secretion of vascular endothelial growth factor A (VEGFA) can promote vascularization of BAT itself, and increase thermogenesis [111]. Chemokine C-X-C motif chemokine ligand-14 (CXCL14) is a novel regulatory factor secreted by BAT in response to thermogenic activation. CXCL14 promotes adaptive thermogenesis via M2

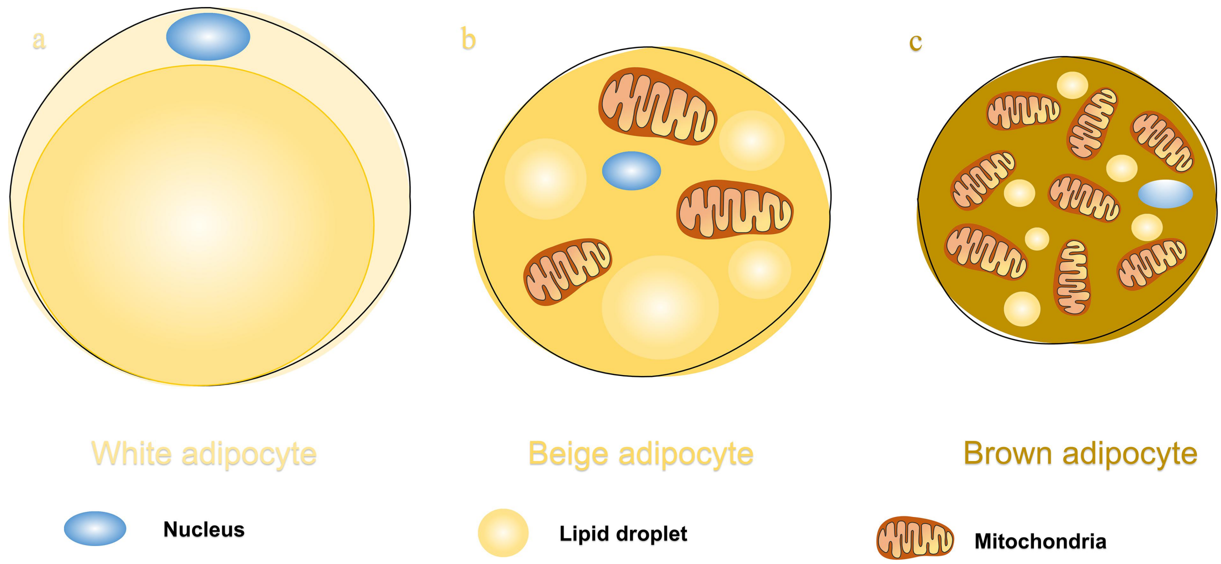

Figure 2. a. White adipocytes contain large unilocular lipid droplets and few mitochondria, and their main function is to store energy. In humans, WAT is mainly found in visceral adipose tissue and abdominal subcutaneous adipose tissue; b. Beige adipocytes contain moderate amounts of lipid droplets and mitochondria, which can express UCP1 thermogenesis, but it's reversible; c. Brown adipocytes contain multilocular lipid droplets and many mitochondria expressing UCP1, which can burn fat and produces heat. BAT is mainly found in the interscapular and subclavian.

macrophage recruitment, BAT activation and the browning of white fat [113,114].

In mice exposed to cold β-adrenergic stimulation, causes a significant induction of FGF21 mRNA levels in BAT, and FGF21 increases glucose uptake in adipocytes [115,116]. FGF21 induces browning of WAT and activation of brown adipocytes in mice [117,118]. Adipose-specific deletion of the FGF21 coreceptor KLB renders mice unresponsive to β-adrenergic stimulation. In contrast, mice with liver-specific ablation of FGF21 show no change [119,120]. Combined, these results indicate the autocrine role of FGF21 in adipocytes. In obese and type 2 diabetic mice, reduced levels of KLB decreased the thermogenic responsiveness of adipose tissue to cold exposure. These impairments in obese mice can be reversed by exercise, which sensitizes the action of FGF21 in adipose tissue and maintains metabolic homoeostasis [120,121].

BMPs also play an important role in the differentiation of adipogenesis. It is believed that BMP4 can trigger the commitment of stem cells to the white adipocyte lineage [122]. BMP7 promotes the formation of brown fat in mice [123]. Activation of BAT requires the involvement of the regulators PRDM16 and PGC-1α (PPAR-γ coactivator-1α), and BMP7 induces this process and increases the expression of UCP1 and C/EBPα, thereby promoting BAT formation [123,124]. However, there is evidence of differences between mice and humans. In humans, both BMP4 and BMP7 act in adipogenesis and WAT to BAT conversion [125,126]. However, BAT activation by BMP7 is temperature-dependent, and it increases BAT volume, activity, and total energy expenditure only at subthermoneutrality, suggesting that intact sympathetic activation is a prerequisite for the effects of BMP7 on BAT [127].

Regulation of adipokines in chronic inflammation

Obesity can induce chronic low-grade inflammation [128], which leads to insulin resistance and diabetes-related vascular complications. Obesity increases lipopolysaccharide (LPS) in the intestinal flora, which initiates the inflammatory cascade by activating pattern recognition TLR4 and leads to insulin resistance [129,130]. WAT secretes anti-inflammatory and proinflammatory factors. Adipose tissue inflammation is initiated and sustained by dysfunctional adipocytes secreting inflammatory adipokines and infiltration of myelo-derived inflammatory cells [131]. In this process, macrophages regulate inflammatory signalling cascades in the tissue. A study in obese mice showed that obesity induces the local expansion of resident intraislet macrophages, which may contribute to the restriction of insulin secretion and impairment of islet cell function [132,133]. In addition, glycogen metabolism is also involved in the regulation of macrophage-mediated acute inflammatory responses.

C-reactive protein (CRP), tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are typical proinflammatory cytokines that destroy islet cell cells and weaken insulin sensitivity. Adiponectin is negatively correlated with the inflammatory factors CRP and IL-6 and inhibits TNF-α production. M1 macrophages stimulate proinflammatory factors and induce insulin resistance, while M2 macrophages block the inflammatory response and promote oxidative metabolism. Adiponectin exerts anti-inflammatory effects by inhibiting M1 and stimulating M2 macrophages. In addition, adiponectin induces IL-10 and reduces proinflammatory cytokines in human macrophages [134–136]. CTRPs are structurally similar to adiponectin and thus harbour a similar function [18,137,138]. Omentin-1 also inhibits the expression of LPS-induced inflammatory factors in macrophages, and it exerts anti-inflammatory effects through the p38, JNK, ERK, and nuclear factor kappa B (NF-κb) signalling pathways [100,139]. However, the underlying mechanism needs further investigation.

In addition, angiotensin- [1–7] (Ang1–7) and BMP7 [140,141] also exert anti-inflammatory effects by inhibiting oxidative and various inflammatory signalling pathways, such as p38 and p44/42 MAPK. These studies provide more possibilities for the treatment of diabetes complications (such as diabetic nephropathy, diabetic retinopathy, and atherosclerosis).

Adipokines and appetite

Obesity has become a worldwide problem, and a strong appetite is an important cause of obesity. Studies of appetite-suppressing factors and appetite-promoting factors have provided new ideas for the clinical treatment of obesity and anorexia.

Leptin suppresses appetite by acting on the hypothalamus. Leptin binds to pro-opiomelanocortin (POMC) neuronal surface receptors and stimulates the release of alpha-melanocyte-stimulating hormone (α-MSH). Then, α-MSH binds to the melanocortin-4 receptor (MC4R) and sends signals to the paraventricular nucleus (PVN), thereby suppressing appetite and reducing energy intake, and disruption of the PVN can lead to binge eating [142–144]. As early as 1999, a study showed that exogenous leptin administration resulted in weight loss in adults [145]. However, the leptin levels of most obese people are significantly higher than those of normal people, and they usually show leptin resistance because of high-fat diet-induced obesity disrupting multiple regions of the hypothalamus and affecting melanocortin signalling [146]. In brain tissue, once the leptin receptor is activated, it recruits the tyrosine kinase JNK-2 and phosphorylates tyrosine residues, resulting in the activation of extracellular signal regulation and recruitment of SOCS-3, which inhibits leptin signalling. As such, hyperleptinemia in obese patients may trigger brain leptin resistance via activation of SOCS-3 [35]. Signal transducer and activator of transcription (STAT) 3 is a key factor in the anorexic effect of leptin. ERK, STAT5 and PI3K are also involved in the regulation of hypothalamic appetite, while SOCS3 and protein tyrosine phosphatase-1B (PTP1B) are negative regulators of leptin signalling [147,148]. Deficiency of PTP1B signalling also increases leptin sensitivity and reduces obesity [149]. Many other mechanisms contribute to leptin resistance, such as impaired blood-brain barrier transport, competitive leptin inhibition, endoplasmic reticulum stress, and impaired ERK signalling [150,151]. In this case, a decrease in plasma leptin levels restores hypothalamic leptin sensitivity and leads to reduced food intake, increased energy expenditure and improved insulin sensitivity [152].

Some factors can influence eating by modulating leptin. Agouti-related peptide (AgRP) is a neuropeptide produced in the brain by AgRP/neuropeptide Y (NPY) neurons. It acts as an antagonist of MC4R that promotes feeding and obesity. Under starvation, circulating leptin and insulin levels decrease, and sustained NPY signalling enables AgRP neurons to drive feeding [146,153]. Hypothalamic T-cell protein tyrosine phosphatase (TCPTP) is induced by fasting and is broken down after feeding. TCPTP controls insulin receptor signalling in AgRP neurons in response to feeding and glucose uptake [154]. TCPTP and PTP1B inhibitors may improve leptin sensitivity and reduce obesity [149,155]. Ghrelin is a brain-gut peptide that promotes growth hormone secretion and enhances appetite, and targeting it may benefit patients with depression and anorexia nervosa [156].

Conclusion and further perspectives

Disorders of glucolipid metabolism are closely related to obesity and insulin resistance, and the underlying mechanisms include inflammation, appetite, and white fat browning, with multiple adipokines involved in this process. In this review, we summarized the regulation of glucolipid metabolism and the role of several major adipokines (Table 1), and a better understanding the role of adipokines in endocrine metabolism is necessary.

In addition to these peptide adipokines, adipose tissue also secretes nonpeptide secreted factors, which are disseminated in the blood, called lipokines, such as lysophosphatidic acid (LPA) and palmitoleic acid. Such factors are also closely related to insulin resistance, insulin sensitivity, fat metabolism and energy expenditure.

Table 1. A summary of the role of adipokines on glycolipid metabolism.

Adipokines	Roles and Mechanisms in Glycolipid Metabolism
Adiponectin	Activate AMPK and MAPK, stimulate GLUT4 translocation and glucose uptake [11][V].
	Positive correlation with HDL [48][III], negative correlation with TG and VLDL [52][III].Increases HDL assembly and accelerates reverse cholesterol transport [50][V].
	APPL1 binds AdipoR1/R2 to activate downstream signalling pathways including glucose uptake, fatty acid oxidation, and insulin signalling [14][V].
	Inhibit M1 and stimulate M2 macrophages [136][V]; Induce IL-10 and reduce pro-inflammatory cytokines in human macrophages [135][V].
FGF21	Increase adiponectin levels to regulate glucolipid metabolism [19][V].
	Induce browning of WAT and activate brown adipocytes [117][V].
	Moderate simple sugar intake and preferences for sweet foods via signalling with FGF21 receptors in the paraventricular nucleus of the hypothalamus [31][II].
Leptin	Inhibit hepatic gluconeogenesis and promote glucose uptake [37][V]; Increase insulin sensitivity and improve glucose utilization [38][V].
	Physiologic leptin replacement suppresses lipolysis and reduces plasma glucose, but supraphysiologic leptin stimulates lipolysis and increases plasma glucose [39][V].
	Exogenous leptin administration resulted in weight loss in adults [145][I].
	Appetite control by the leptin-POMC pathway [144][V].
CTRPs	CTRP9 is structurally similar to adiponectin and exerts similar effects as adiponectin [17][V].
	CTRP6 regulates adipocyte proliferation and differentiation [58][V]. Knockdown of CTRP6 reduces the deposition of fatty tissue [59][V].
	CTRP3 concentration was positively correlated with HDL, but negatively with TG and VLDL [61][V].
BMPs	BMP4 is capable of triggering commitment of stem cells to the white adipocyte lineage [122][V].
	BMP7 promotes the formation of brown fat in mice [123][V].
	In humans, both BMP4 and BMP7 act in adipogenesis and WAT to BAT conversion [125][V].
Adipsin	Preserve beta cells and ameliorate hyperglycaemia in diabetic mice [3][V].
	Increases triglyceride synthesis in adipocytes and inhibit lipolysis [6][III].
Resistin	Inhibits hexokinase activity and reduces glucose uptake [13][V].
	Induces an inflammatory response through the TLR4 signalling pathway, leading to insulin resistance [93][V].
IGFBP2	Induce GLUT-4 translocation and glucose uptake [42][V].
	Inhibit human visceral adipogenesis and lipogenesis [64] [V].
	Negatively correlated with VLDL and TG levels [66][III].

Abbreviations: AMPK, AMP-activated protein kinase; MAPK, mitogen-activated protein kinase; GLUT4, glucose transporter type 4; HDL, high-density lipoprotein; TG, triglyceride; VLDL, very low-density lipoprotein; APPL1, adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1; AdipoR1/R2, adiponectin receptor 1 and adiponectin receptor 2; M1, M1 macrophages; M2, M2 macrophages; IL-10, interleukin-10; WAT, white adipose tissue; FGF21, fibroblast growth factor-21; POMC, pro-opiomelanocortin; CTRP, C1q/TNF-related protein; BMP, bone morphogenetic protein; BAT, brown adipose tissue; TLR4, toll-like receptors 4; IGFBP-2, insulin-like growth factor binding protein-2. I-V are graded according to the rank of Evidence-Based Medicine (EBM). I: systematic reviews, meta analyses, randomized control trials; II: cohort studies; III: case control studies; case reports; IV: ideas, expert opinions; V: animals researches, in vitro experiments.

Increasing research on adipokines is expected to make them valuable in disease prediction, therapeutic targeting, and prognostic assessment. However, the current studies on adipokines are not sufficient, and there are still many shortcomings in the study of adipokine production, secretion, interaction and mechanisms of metabolic regulation; more unknowns are waiting to be discovered. In the future, adipokine-based drugs may become potentially novel and innovative therapeutic approaches for the treatment of metabolic diseases.

Disclosure statement

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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