Cerrahpaşa Med J 2025; 49: 1-15 REVIEW

Well-Known and Novel Adipokines as Metabolic Orchestrators: From Pathophysiological Insights to Therapeutic Perspectives

Esma Nur Şeker[1], Muhammed Yusuf Afacan[2,3], Selin Kahraman[1], Karolin Yanar[1], Seval Aydın[1]

[1]Department of Medical Biochemistry, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye
[2]Department of Orthopaedics and Traumatology, İstanbul Physical Therapy and Rehabilitation Training and Research Hospital, İstanbul, Türkiye
[3]Department of Anatomy, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Institute of Graduate Studies, İstanbul, Türkiye

Cite this article as: Şeker EN, Afacan MY, Kahraman S, Yanar K, Aydın S. Well-known and novel adipokines as metabolic orchestrators: from pathophysiological insights to therapeutic perspectives. *Cerrahpaşa Med J.* 2025, 49, 0098, doi: 10.5152/cjm.2025.25098.

Abstract

Adipokines are bioactive signaling proteins predominantly secreted by active metabolic and endocrine organ—white adipose tissue—and serve as metabolic orchestrators linking inflammation, appetite regulation, insulin sensitivity, energy metabolism, and cognitive function. Adipokines are categorized into 2 groups: well-known adipokines such as leptin, adiponectin, orexin, apelin, visfatin and novel adipokines including irisin, C1q tumor necrosis factor-related proteins, subfatin, isthmin, vaspin, etc. Novel adipokines are being identified day by day, resulting in a growing variety of adipokines. Adipokines that function at both local and systemic levels can have either pro-inflammatory or anti-inflammatory effects depending on their functionally diverse complex signaling pathways including Janus kinases/signal transducer and activator of transcription proteins, 5′-adenosine monophosphate-activated protein kinase (AMPK), phosphoinositide 3-kinase / protein kinase B, mitogen-activated protein kinase, and toll-like receptor 4. Disruption of systemic homeostasis triggers overproduction of adipokines and facilitates the development of pathological conditions and metabolic and cardiovascular, skeletal, neurodegenerative and eating diseases/disorders, such as obesity, insulin resistance, type 2 diabetes, cardiovascular diseases, osteoarthritis, multiple sclerosis, and Alzheimer's disease. Comprehending the structures, mechanisms, and actions of adipokines is crucial for identifying potential therapeutic targets. Modulation of adipokine profiles through pharmacological interventions may represent a promising strategy for enhancing metabolic health. This comprehensive review highlights the fundamental roles of classical and novel adipokines in health and disease and advocates for further research into their diagnostic and therapeutic potential.

Keywords: Adipokines, adipose tissue, inflammation, leptin, metabolic diseases, therapeutic targets

Introduction

Adipose tissue is one of the metabolically active endocrine tissues, which is divided into 5 types: white adipose tissue (WAT), brown adipose tissue (BAT), beige adipose tissue, marrow adipose tissue (MAT), and pink adipose tissue. Their location, characteristics, and functions are different. The BATs are ellipsoidal cells that are extensively spread in the interscapular area. These cells include tiny and numerous fat droplets and high amounts of mitochondria, similar to beige adipocytes. The BATs are referred to as thermogenic tissues. Upon stimulation, these tissues express uncoupling protein 1 (UCP1), like beige adipocytes. These tissues enhance insulin sensitivity, regulate energy homeostasis and prevent fat accumulation, promote overall fat oxidation, and stimulate diet-induced thermogenesis. Brown adipose tissue activity peaks during winter and decreases in summer. Beige adipocytes are distributed beneath the skin adjacent to the spine and the collarbone in adults. They store energy and are responsible for heat generation. The MAT is located in the bone marrow cavity. These adipocytes manage hematopoietic homeostasis and osteogenesis. Pink adipocytes originate from WAT during pregnancy and lactation. These adipocytes exhibit a structure more characteristic of epithelial cells. They also contain peroxisomes and rough endoplasmic reticulum.

Received: November 8, 2025 **Revision Requested:** November 22, 2025 **Last Revision Received:** November 23, 2025
Accepted: November 27, 2025 **Publication Date:** December 31, 2025
Corresponding author: Seval Aydın, Department of Biochemistry, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Institute of Graduate Studies, İstanbul, Türkiye
e-mail: seval.aydin@iuc.edu.tr
DOI: 10.5152/cjm.2025.25098

These adipocytes are responsible for the production and secretion of milk. White adipose tissue is predominantly located in the subcutaneous tissue and surrounding the body's visceral organs. These cells are spherical and have bigger and single fat droplets that displace other organelles and lower mitochondria, like pink and MAT. The WATs are the predominant adipocytes responsible for energy storage and distribution, regulate insulin sensitivity and feeding behavior, and adipokine secretion. The adipocytes in WAT contain large amounts of triglycerides (TGs), which are stored in the form of lipid droplets. In addition, WAT is composed of adipocytes, adipocyte precursors, leukocytes, and endothelial cells. Changes in the body's energy balance directly affect TG stores within adipocytes, indicating a positive correlation between body weight and total fat mass. During prolonged fasting, lipolysis is activated in WAT, thereby providing the energy required for the body. When energy intake is excessive, lipogenesis is activated in WAT, resulting in an increase in TG synthesis. This indicates that WAT is a dynamic organ that continuously regulates the balance of energy intake, expenditure, and storage according to the body's energy requirements. In addition, WAT regulates not only energy balance but also various physiological processes through a number of adipokines it secretes. Therefore, WAT is also referred to as an endocrine organ.[1,2]

Classification of Adipokines

Adipokines, whose existence was fully confirmed in 1994, are known to exert both local (autocrine/paracrine) and systemic (endocrine) effects. It has been demonstrated that adipokines mediate communication between adipose tissue and peripheral tissues, thereby influencing various physiological processes.[3,4]

Adipokines are classified according to their discovery date and their functions in inflammation. According to their discovery date, adipokines are classified into 2 groups as well-known (Table 1) and novel identified (Table 2) adipokines, whereas based on their inflammatory functions, they are categorized as pro-inflammatory and anti-inflammatory adipokines. Some of the adipokines can show both pro-inflammatory and anti-inflammatory properties, depending on their amount.

Well-Known Adipokines

Leptin

Leptin is a protein-structured hormone with 167 amino acid residues primarily secreted by adipose tissue and the hypothalamus, as well as other peripheral tissues.

Leptin synthesis, influenced by circadian rhythm, reaches its highest levels around midnight and the early morning hours, while its levels are lowest around noon and the afternoon. Due to a higher body fat percentage, obese individuals have elevated serum leptin concentrations compared to lean individuals. Additionally, among individuals of similar age and weight, women produce more leptin than men. Leptin levels are higher during the luteal phase in women, but lower during menopause. Thus, leptin concentration is influenced not only by body weight but also by sex and fluctuating levels of sex hormones such as estrogen and testosterone.[5]

Leptin acts by binding to leptin receptors (LepR) in the hypothalamus and peripheral tissues. The longest isoform of the receptor is mainly expressed in the brain. Leptin binding activates the LepR–Janus kinase 2 (JAK2) complex, leading to phosphorylation of receptor tyrosine residues and subsequent phosphorylation of signal transducer and activator of transcription 3 (STAT3) and STAT5. Activated STATs dimerize, enter the nucleus, and increase the transcription of anorexigenic genes such as proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript.

Table 1. Well-Known Adipokines Belonging to the Pro-Inflammatory or Anti-Inflammatory Groups

Well-known Adipokines	
Anti-inflammatory Adipokines	**Pro-inflammatory Adipokines**
IL-10	TNF-α
ApN	IL-1β
Orexin	IL-6
Apelin	Apelin
Visfatin	Visfatin
	Leptin

ApN, adiponectin; ASP, acylation stimulating protein; IL-10, interleukin-10; IL-1β, interleukin-1β; IL 6, interleukin-6; TNF-α, tumor necrosis factor-α.

Post-translational modification of POMC leads to the formation of α-melanocyte-stimulating hormone, which interacts with its receptor to transmit a satiety signal to the brain, thereby inhibiting appetite.[6] Concurrently, leptin suppresses the expression of orexin, agouti-related peptide (AgRP), and neuropeptide Y (NPY), further contributing to appetite reduction. Collectively, these effects enhance energy expenditure and decrease body mass.[7]

Leptin also modulates metabolism by activating 5′-adenosine monophosphate-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC). Additionally, JAK2 interacts with the Src homology 2 domain of growth factor receptor-bound protein 2 (Grb2), activating the mitogen-activated protein kinase (MAPK) signaling cascade involving extracellular signal-regulated kinase (ERK) (Raf), mitogen-activated protein kinase kinase (MEK), and ERK.

Moreover, JAK2 phosphorylates insulin receptor substrate, thereby activating the phosphoinositide 3-kinase (PI3K)–protein kinase B (Akt) signaling pathway. This pathway stimulates ATP-sensitive potassium channels and voltage-gated calcium channels and also increases the transcription of POMC genes.

To prevent excessive signaling, the suppressor of cytokine signaling 3 binds to phosphorylated tyrosine residues on JAK2, blocking STAT recruitment or directly inhibiting JAK2 activity. This

Table 2. Novel Adipokines Belonging to the Pro-Inflammatory or Anti-Inflammatory Groups

Novel Adipokines	
Anti-inflammatory Adipokines	**Pro-inflammatory Adipokines**
Irisin	ASP
CTRPs	CTRPs
Subfatin (METRNL)	Resistin
ISM-1	Asprosin
Vaspin	Chemerin
Nesfatin-1	

CTRPs, C1q/TNF-related proteins; ISM1, isthmin-1; METRNL, meteorin-like protein.

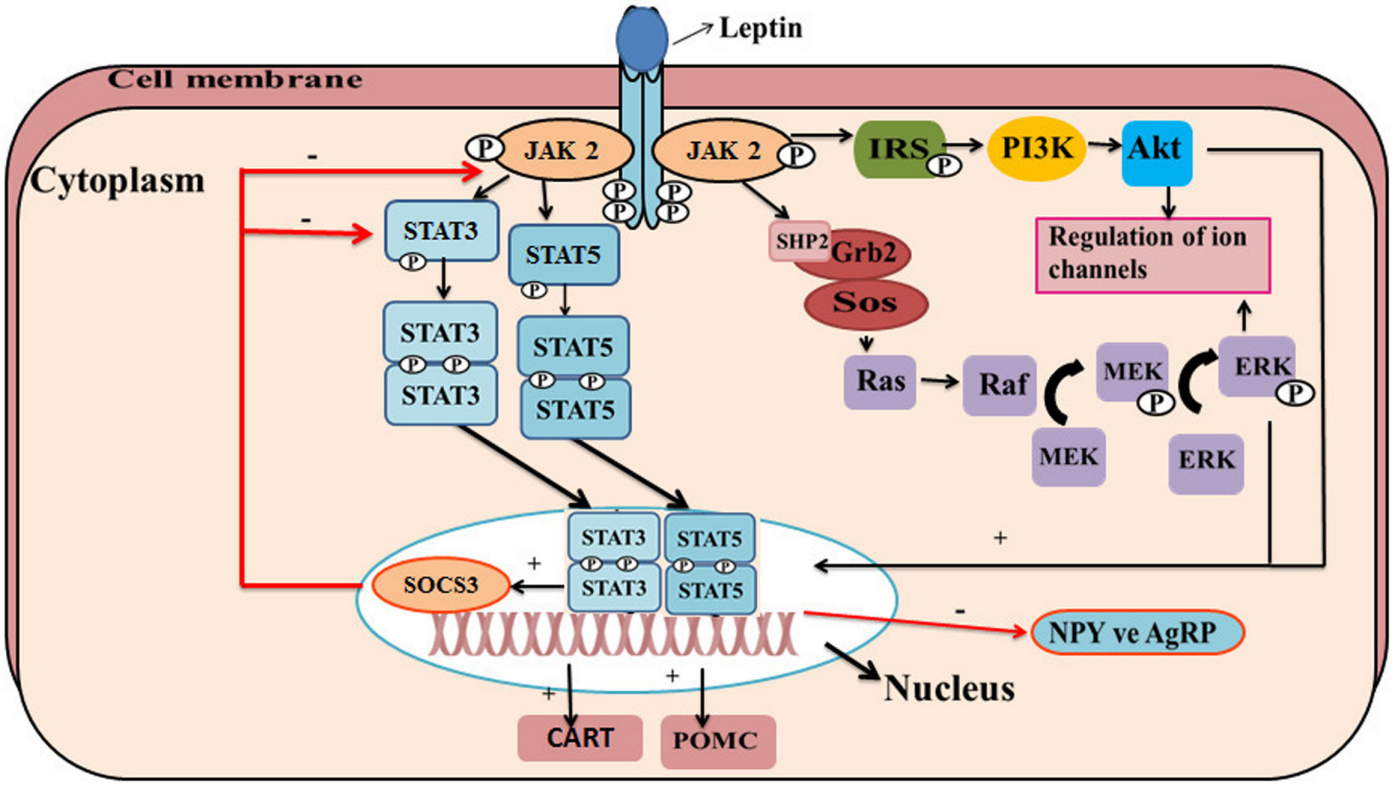

Figure 1. Leptin signaling pathway. AgRP, agouti-related peptide; Akt, protein kinase B; CART, cocaine- and amphetamine-regulated transcript; ERK, extracellular signal-regulated kinase; Grb2, SH2 (Src homology 2) domain of growth factor receptor-bound protein 2; IRS, insulin receptor substrate; MEK, activating the mitogen-activated protein kinase kinase; NPY, neuropeptide Y; POMC, proopiomelanocortin; PI3K, phosphatidylinositol 3-kinase; Raf, MAP kinase; Sos, guanosine nucleotide exchange factor; STATs, signal transducer and activator of transcription proteins; SOCS3, suppressor of cytokine signaling 3; SHP2, SH2-containing protein tyrosine phosphatase 2; JAK2, Janus kinase 2.

negative feedback loop attenuates leptin signaling via the JAK2/STAT3 pathway and helps maintain leptin homeostasis (Figure 1).[6]

Leptin regulates thermogenesis by stimulating the norepinephrine β3-adrenergic receptor in adipose tissue, promoting fatty acid oxidation and the synthesis of UCPs. During states of undernutrition, reduced leptin concentrations activate various energy-conserving mechanisms essential for maintaining vital functions. The first of these mechanisms is the reversal of thermogenic processes, leading to a slowdown in fatty acid oxidation. Leptin also reduces thyroid hormone secretion in the hypothalamus, thereby lowering metabolic rate, and inhibits the synthesis of sex hormones, which suppresses reproductive activity and reduces energy expenditure. It enhances the synthesis of growth hormone and glucocorticoids, which activate energy reserves in the body to supply the energy required for sustaining vital physiological functions. Leptin regulates reproduction, body temperature, energy balance, appetite, glucose and lipid metabolism. Leptin has neuroprotective and cognitive effects on the hippocampus (Figure 2).[5-7]

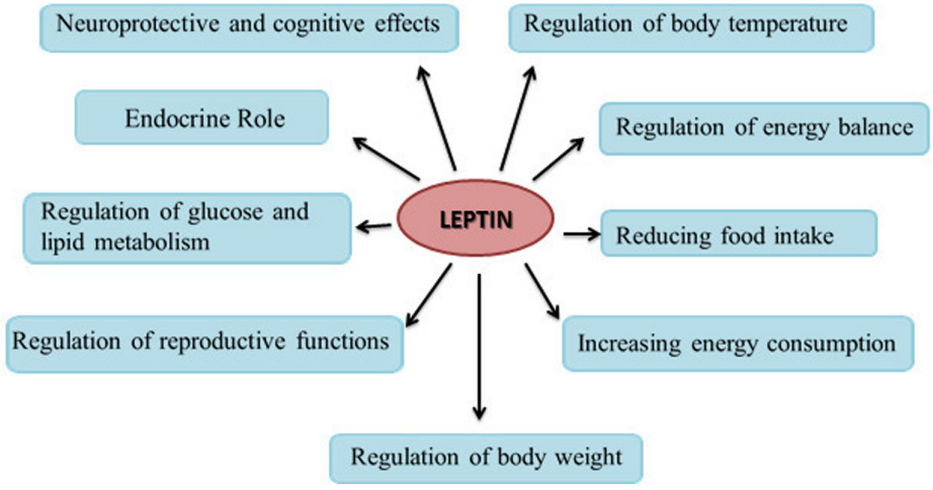

Figure 2. Functions of leptin.

Adiponectin

Adiponectin (ApN) is a 224 amino-acid protein produced by WAT.In the circulation, ApN exists in 3 structural forms: trimers, hexamers, and high-molecular-weight multimers. Typically, ApN circulates predominantly in hexameric (2 trimers) or multimeric (6 trimers) forms. Additionally, ApN may be present at low levels in a proteolytically cleaved, globular monomeric form.

Adiponectin exerts its action through 2 specific receptors: AdipoR1 and AdipoR2. Both AdipoR1 and AdipoR2 are expressed in the liver, muscle, and adipose tissues. Additionally, AdipoR1 is synthesized by synovial fibroblasts in skeletal muscle, as well as by endothelial and atrial cells. AdipoR1 exhibits high affinity specifically for the globular form of ApN. In contrast, AdipoR2, predominantly expressed in hepatic tissue, binds with high affinity to the trimeric, hexameric, and multimeric forms of ApN. Adiponectin plays a central role in regulating energy homeostasis, inflammatory responses, insulin sensitivity, and fatty acid oxidation (Figure 3).[8]

Adiponectin crosses the blood–brain barrier and regulates several essential physiological functions, including systemic energy homeostasis, neuronal biosynthesis in the hippocampus, and synaptic plasticity.[8,9] In the liver, ApN suppresses fatty acid synthesis and gluconeogenesis, while in both muscle and liver tissues, it enhances glucose uptake, glycolysis, and fatty acid oxidation. Through the AdipoR1 signaling pathway, activation of AMPK suppresses the gene-level transcription of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase. Additionally, AMPK inhibits ACC crucial for fatty acid biosynthesis by phosphorylating it. This inhibition reduces the levels of malonyl-CoA, thereby slowing fatty acid synthesis. The reduction in malonyl-CoA removes this inhibitory effect, facilitating the mitochondrial uptake and subsequent oxidation of free fatty acids. The AMPK also inhibits sterol regulatory element-binding protein 1c, a key regulator of lipogenesis, through phosphorylation.[8] Meanwhile, the AdipoR2 signaling pathway activates peroxisome proliferator-activated receptor alpha (PPAR-α), which promotes fatty acid oxidation.[9] In skeletal muscle, ApN binds to AdipoR1; this interaction leads to the activation of protein kinase C (PKC). The PKC increases intracellular Ca^{2+} influx, thereby activating calcium/calmodulin-dependent protein kinase kinase (CaMKK).[8] Additionally, ApN enhances insulin sensitivity in muscle by regulating the p38 MAPK and PPAR-α signaling pathways, thereby promoting fatty acid oxidation. It also increases glucose transport into cells by stimulating glucose transporter type 4 (GLUT4) translocation in both muscle and adipose tissues.[9] In the heart, ApN binds to AdipoR1 and promotes the translocation of cluster of differentiation 36 (CD36) in cardiomyocytes, leading to enhanced fatty acid uptake, Akt phosphorylation, improved insulin sensitivity, and increased glucose uptake. Furthermore, activated AMPK in cardiac tissue phosphorylates and inhibits ACC, resulting in enhanced oxidative phosphorylation. In the kidney, ApN exerts its effects through both AdipoR1 and AdipoR2. Renal AMPK activation by ApN provides antioxidant effects and suppresses inflammation. In bone tissue, ApN receptors are expressed both in primary osteoblasts and bone marrow macrophages. By interacting with these receptors, ApN promotes the differentiation of osteoclasts (Figure 4).[8,9]

Apelin

Apelin is an adipokine synthesized as a 77-amino acid long preproapelin. This precursor is cleaved by the endonuclease FURIN to generate proapelin, a 55-amino-acid peptide, which is further processed into apelin-36, apelin-17, apelin-16, and apelin-13 isoforms. These apelin peptides exert biological activity by binding to their specific receptor. Apelin is synthesized in various human tissues including the brain, heart, lungs, kidneys, liver,

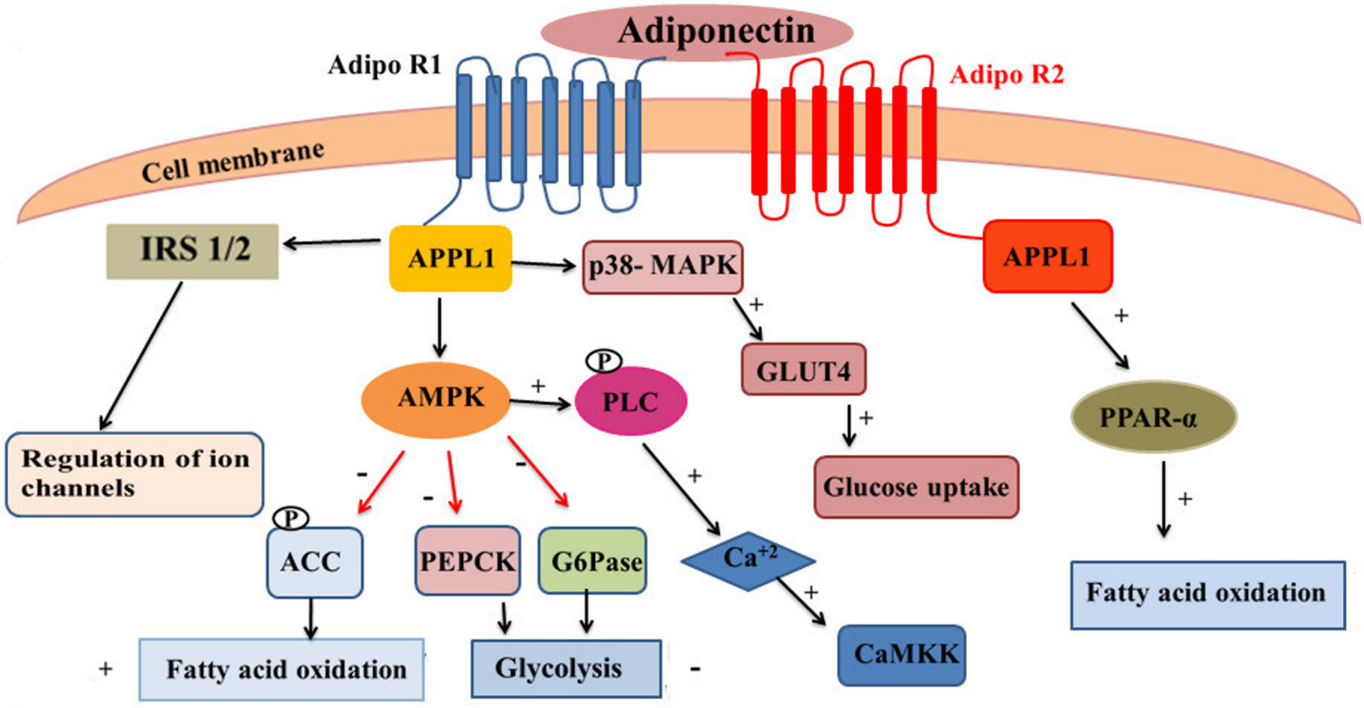

Figure 3. Placement of adiponectin receptors AdipoR1 and AdipoR2 within the cell membrane and the signaling pathways activated by each receptor. ACC, acetyl-coa carboxylase; APPL1, adaptor protein containing pH domain and leucine zipper 1; AMPK, 5′-adenosine monophosphate-activated protein kinase; CaMKK, calcium/calmodulin-dependent protein kinase kinase; Ca, calcium; G6Pase, glucose-6-phosphatase; GLUT, glucose transporter; IRS, insulin receptor substrate; PEPCK, phosphoenolpyruvate carboxykinase; p38-MAPK, p38-mitogen-activated protein kinase; PPAR-α, peroxisome proliferator-activated receptor alpha; PLC, phospholipase C.

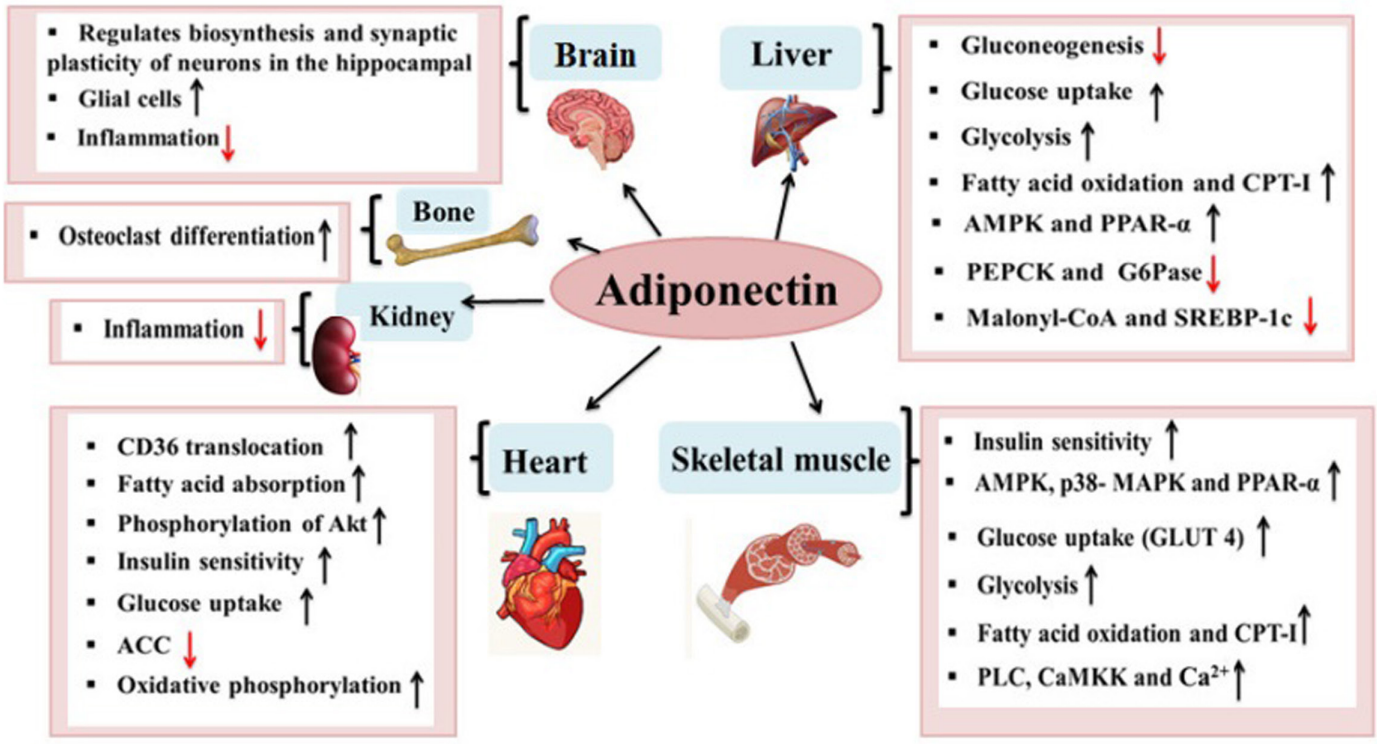

Figure 4. Functions of adiponectin in tissues. AMPK, 5′-adenosine monophosphate-activated protein kinase; ACC, acetyl-coa carboxylase; Akt, protein kinase B; CaMKK, calcium/calmodulin-dependent protein kinase kinase; Ca^{2+}, calcium; CD36, cluster of differentiation 36; CPT-I, carnitine palmitoyl transferase I; G6Pase, glucose-6-phosphatase; GLUT, glucose transporter; PEPCK, phosphoenolpyruvate carboxykinase; PLC, phospholipase C; p38-MAPK, p38–mitogen-activated protein kinase; PPAR-α, peroxisome proliferator-activated receptor α; SREBP-1c, sterol regulatory element-binding protein 1c.

breast, pituitary gland, WATe, skeletal muscle, gastrointestinal system, and pancreas.

Its effects in these tissues are mediated via the apelinergic system, consisting of apelin and its receptor. The apelin receptor—also referred to as angiotensin receptor-like 1 (APJ), angiotensin II protein J receptor (APJR), or APLNR—is structurally similar to rhodopsin and belongs to the G protein-coupled receptor (GPCR) family. Activation of the apelin receptor induces the activation of cAMP-dependent protein kinase A. In addition, the activation of GPCRs stimulates other signaling pathways such as phospholipase C beta (PLC-β), PI3K/Akt, and ribosomal S6 kinase 1 (S6K1). Apelin regulates blood pressure, cardiac output, and fluid balance.[10]

Orexin

Orexin is a NP-based adipokine located in the hypothalamus, which regulates various physiological processes including feeding, neuroendocrine functions, and the sleep/wake cycle. Orexins consist of 2 isoforms: orexin A and orexin B, also known as hypocretin 1 and 2, respectively.

In mammals, there are 2 GPCR-family orexin receptors: orexin receptor 1 (OX1R) and orexin receptor 2 (OX2R). The OX1R, expressed in the amygdala and ventromedial hypothalamic nucleus, modulates emotional processing, pain, feeding behavior, and addiction via cholinergic and noradrenergic systems. OX2R is found in histaminergic neurons of the paraventricular nucleus (tuberomammillary nucleus), where it regulates the sleep/wake cycle. Beyond the hypothalamus-pituitary axis, orexin receptors are also expressed in the gastrointestinal tract, endocrine tissues, pancreas, gonads, and other peripheral tissues. They are found in neurons synthesizing NPY and POMC.[11]

Dysregulation of Well-Known Adipokines in Metabolic Disorders

Leptin

Excessive expression of leptin contributes to leptin resistance. This resistance is characterized by the inability of target tissues to adequately respond to leptin despite high circulating leptin levels. As a result, leptin resistance leads to increased appetite and uncontrolled weight gain due to excessive food intake. Moreover, pro-inflammatory cytokines overproduced in obesity contribute further to the development of leptin resistance. Leptin resistance not only contributes to obesity and metabolic syndromes, including type 2 diabetes mellitus (T2DM) and cardiovascular diseases resulting from insulin resistance, but is also linked to neurological disorders such as Alzheimer's disease, Parkinson's disease, dementia, and ischemic stroke.[6] Furthermore, increased leptin promotes chronic inflammation, thereby triggering the development of osteoarthritis in bone.[4]Moreover, increased serum leptin concentrations have been reported in individuals with slipped capital femoral epiphysis.[12]

Adiponectin

Adiponectin levels are reduced in obesity, metabolic syndrome, T2DM, cardiovascular diseases, and cancer.[8] In ApN-deficient mice, insulin resistance develops. Mice lacking the ApN gene eventually develop hepatic steatosis, increased adipocyte differentiation, TG accumulation, and altered insulin sensitivity. Overall, ApN levels are consistently low in obesity and metabolic disorders.[8,9]

Apelin

Apelin has significant effects on energy homeostasis. A decrease in circulating apelin levels contributes to the development of obesity and leads to increased oxidative stress and inflammation.

Apelin deficiency results in hyperglycemia and the development of T2DM. In lipid metabolism, at the physiological level, apelin promotes fatty acid oxidation and inhibits lipogenesis. Reduced apelin levels lead to increased TG and fatty acid concentrations, resulting in hepatic steatosis. Furthermore, apelin deficiency contributes to endothelial dysfunction, hypertension, and the development of cardiovascular diseases.[10]

Orexin

Excessive synthesis of orexin leads to increased appetite and the development of obesity. In addition, since orexin regulates the sleep–wake cycle, overproduction of orexin results in insomnia, whereas insufficient synthesis leads to narcolepsy.[11] Furthermore, studies have shown that orexin and orexin receptor levels increase in response to addiction in the organism.[13]

Orexin A stimulates appetite by acting on the arcuate nucleus of the hypothalamus and is activated during states of hunger and hypoglycemia. Orexin A, which plays a central role in regulating metabolic rate, controls body temperature, non-exercise energy expenditure, arousal, and physical activity, making it an important NP in the fight against obesity.[11]

Therapeutic Implications and Future Perspectives of Well-Known Adipokines

Leptin

Leptin resistance may arise from mutations or deficiencies in the Ob gene, defects in the leptin transporter in circulation, reduced expression of the LepR receptor, or disruptions in LepR signal transduction. Clinical trials have explored combined therapies to overcome leptin resistance.[5] For instance, recombinant methionyl human leptin (r-metHuLeptin/metreleptin) has been administered in clinical studies involving obese individuals to evaluate the relationship between insulin and leptin. Although body weight and circulating inflammatory biomarkers did not change after r-metHuLeptin/metreleptin administration, a reduction in glycated hemoglobin A1c levels was observed in obese hyperleptinemic patients with T2DM.[14] In another study using pegylated human recombinant leptin (PEG-OB), overweight men showed more rapid weight loss when calorie restriction was combined with PEG-OB therapy.[15] In another study involving diet-induced obesity (DIO) in rats, treatment with a combination of amylin and leptin was followed by treatment cessation. Rats subsequently regained their baseline weight more rapidly and gained more weight overall. This suggests that the continued use of combined amylin + leptin therapy may be necessary to maintain weight loss.[16]

Additionally, preclinical studies have shown that leptin stimulates the proliferation of osteoblasts without affecting mature osteoclasts in rats, and that subcutaneous administration of leptin reduces bone fragility.[17] Additionally, in a clinical study conducted in women with hypothalamic amenorrhea, following 36 weeks of meterleptin treatment, a decrease in parathyroid hormone levels and the receptor activator of NF-κB Ligand (RANKL)/ osteoprotegerin ratio were observed, suggesting that meterleptin may reduce osteoclastic activity.[18]

Adiponectin

The ApN concentrations are inversely correlated with insulin resistance in the presence of obesity, metabolic syndrome, and T2DM. In mice lacking the ApN gene, the development of hepatic insulin resistance and an increase in hepatic glucose production have been observed. Furthermore, when these mice were fed a diet rich in saturated fatty acids, the development of carbohydrate intolerance was noted. Subsequently, it was observed that this condition was ameliorated by the acute administration of recombinant ApN.[19] Adiponectin may slow the progression of atherosclerosis by inhibiting foam cell formation and suppressing inflammation in cardiovascular disease by attenuating tumor necrosis factor-alpha (TNF-α) activity. However, because ApN levels are reduced in obese individuals, their risk for cardiovascular disease is significantly higher. The ApN suppresses the spread of cancer cells between tissues, inhibits their growth and proliferation, and induces apoptosis.[8] In a study, ApN levels and AdipoR1 expression were found to be significantly decreased in patients with endometrial cancer.[20] Cancer cells exhibit lower AdipoR1 and AdipoR2 expression compared with normal cells.[8] Another study demonstrated that ApN exerts a significant inhibitory effect on the in vitro proliferation of human pancreatic cancer cells through its receptors.[21] Furthermore, a preclinical study demonstrated that ApN enhances osteoblastogenesis and inhibits osteoclastogenesis in pre-osteoblasts.[22] A clinical study conducted in postmenopausal women with osteoporosis and metabolic syndrome demonstrated that they exhibit significantly lower ApN levels and reduced bone mineral density compared to women with osteopenia.[23]

Apelin

Apelin and its receptor play critical roles in angiogenesis, vasoconstriction, cardiac contractility, and fluid homeostasis.[10]Therefore, considering the role of apelin in the regulation of the cardiovascular system and fluid balance, its therapeutic effects have been investigated. In 1 study, a cyclic analogue, MM07, which activates the Gαi signaling pathway, was developed, and an increase in cardiac output was observed in rat.[24] In another study, chemically modified apelin-17 analogs, P92 and LIT01-196, were shown to significantly improve left ventricular (LV) function after myocardial infarction (MI), reduce heart failure biomarkers, and enhance cardiac contractility as well as sarco/endoplasmic reticulum Ca^{2+}-ATPase-2 (SERCA2) expression. Moreover, this treatment nearly doubled cardiac vascular density and preserved LV wall thickness following MI, while also reducing cardiac fibrosis and fibrosis biomarkers.[25] In addition, a 2RPRL analogue exhibiting competitive antagonism toward APJR was also developed.[10] In a study conducted on rats with a spinal cord injury model, Apelin-13 administration reduced the levels of pro-inflammatory mediators while increasing those of anti-inflammatory mediators. However, silencing of APJ significantly attenuated the effects of Apelin-13 treatment on cytokines.[26] Another study demonstrated that apelin-13 activates AMPK in rats with HDF and promotes GLUT4 translocation in cardiomyoblast membranes, thereby enhancing glucose transport into these cells.[27] In addition, the role of apelin and its receptor in cancer progression and their effects on the reproductive system are highly critical, and therapeutic studies related to apelin are ongoing.[10] Moreover, apelin enhanced osteoblast proliferation and bone healing.[4]

Orexin

Orexin promotes hyperphagia according to the organism's energy requirements. In a study conducted on rats, it was reported that injection of orexin A increased appetite, whereas in another group of rats, appetite was suppressed following injection of the OX1R antagonist SB-334867.[28] In neuroanatomical studies, orexin has been shown to stimulate cholinergic neurons, thereby promoting wakefulness in the organism. A study has shown that mice deficient in OX2R exhibit narcolepsy. In this experiment, OX2R-selective agonists were reported to alleviate narcoleptic

symptoms.[29] Additionally, orexin activates reward pathways by increasing the activity of both dopaminergic and non-dopaminergic neurons associated with addiction. In a study, chronic morphine administration was shown to enhance the activity of dopaminergic neurons and induce anxiety-like behaviors in mice. Following administration of the OX1R antagonist SB334867, it was indicated that OX1R plays a critical role in anxiety-like behaviors emerging during prolonged abstinence from morphine. Therefore, the use of orexin receptor antagonists or the inhibition of orexin release may serve as a therapeutic approach for addiction.[13] In another study, SB334867, a selective OX1R antagonist, was administered to social and non-social mice. In non-social mice, it did not alter social behavior but was found to reduce stress and depression-like behaviors.[30]Consequently, a thorough understanding of the orexin system and detailed investigation of how its levels change under different pathological conditions are necessary to develop a therapeutic approach with appropriate dosage and duration.

Other Well-Known Adipokines

The structures, tissues of synthesis, receptors, signaling pathways, pathological and pathophysiological roles, and therapeutic effects of other well-known adipokines are presented in Table 3.

Table 3. Overview of Other Well-Known Adipokines: Biochemical Characteristics and Physiological–Pathophysiological Roles, and Therapeutic Effects

Adipokine	Sites of Synthesis	Receptors	Signaling Pathway	Physiological Roles	Pathophysiological Roles	Therapeutic Effect
TNF-α	Macrophages, muscle cells, lymphocytes	TNF-R1 TNF-R2	NF-κB PI3K/ Akt MAPK (p38, JNK, ERK)	It contributes to host defense against infections	Pro-inflammatory Apoptosis Insulin resistance Cytokine and ROS production	TNF-α inhibitors are used to suppress chronic inflammatory conditions In infection and sepsis, TNF-α blockade is employed[31]
IL-6	Myocytes, adipocytes, immune and endothelial cells	IL-6Rα	JAK/STAT3	It exerts acute-phase response, immune regulation, hematopoiesis, insulin sensitivity, glucose, and FFA oxidation, leptin regulation	Multiple myeloma Rheumatoid arthritis (RA) Castleman's disease Psoriasis Cancer Osteoporosis	IL-6 inhibitors are used in inflammatory, metabolic, and autoimmune diseases[32]
IL-1β	Macrophages, adipocytes	IL-1R1 IL-1R2	NF-κB MAPK	It plays a central role in immune proliferation, hematopoiesis, antibody production, tissue repair, while also inhibits adipocyte differentiation	Insulin resistance Obesity	IL-1β inhibitors are used in inflammatory, autoimmune, and cardiovascular diseases[33]
IL-10	M2 macrophages, Th2 lymphocytes, adipocytes	IL-10Rα	JAK1/ TYK2 JAK/ STAT3	It is anti-inflammatory; suppresses pro-inflammatory cytokines and immune responses, and regulates glucose/lipid metabolism	Autoimmune diseases Impaired immunity Cancer	IL-10 is used as an anti-inflammatory, autoimmune, and immunoregulatory agent[34]
Visfatin (NAMPT)	Lymphocytes, bone marrow, liver, kidney, adipocytes, heart, and muscle tissue	TLR4 INSR	NF-κB NAD⁺–SIRT1 MAPK/ ERK1/2 JAK/ STAT AMPK PI3K/Aktæ	Increases glucose uptake and regulates blood sugar Regulates energy homeostasis, the nervous system, CVD, tissue repair, and antioxidant mechanisms It is effective in NAD⁺ biosynthesis, DNA repair, and sirtuin activity It regulates cell growth and differentiation and modulates the immune response	Obesity T2DM CVD Pro-inflammatory Cancer Neurological diseases PCOS	Inhibition of visfatin may have a therapeutic role in the pathology of RA[4,35]

AMPK, 5′ adenosine monophosphate-activated protein kinase; Akt, protein kinase B; BAT, brown adipose tissue; CVD, Cardiovascular diseases; ERK, extracellular signal-regulated kinase; IL-6, interleukin 6; IL-1β, interleukin-1 beta; IL-10Rα, interleukin-10 receptor alpha; IL-1R1, interleukin-1 receptor type 1; IRS, insulin receptor substrate; INSR, insulin receptor; JAK, Janus kinases; MAPK, mitogen-activated protein kinase; NAMPT, nicotinamide phosphoribosyltransferase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NAD , nicotinamide adenine dinucleotide; SIRT, sirtuin; STAT, signal transducer and activator of transcription proteins; PIN1, peptidyl-proline isomerase 1; PI3K/Akt, phosphoinositide 3-kinase / protein kinase B; RA, rheumatoid arthritis; ROS, reactive oxygen species; TNF-α, tumor necrosis factor α; TNF-R, tumor necrosis factor receptor; TLR, toll-like receptor; TYK2, tyrosine kinase 2; WAT, white adipose tissue.

Novel Adipokines

Acylation Stimulating Protein

Acylation stimulating protein (ASP), also known as C3adesArg, is a complement system protein synthesized and secreted by adipocytes.

The ASP receptor, C5L2, belongs to the GPCR family and is grouped with receptors for C5a, C3a, and N-formylmethionyl-leucyl-phenylalanine. The ASP binds with high affinity to this receptor, enhancing glucose transport into cells. A study has shown that the ASP receptor activates the PI3K signaling pathway. ASP also activates the MAPK/ERK1/2, cytosolic phospholipase A2, and PKC enzymes.[36]

Asprosin

Asprosin is a 140-amino-acid orexigenic adipokine. Asprosin binds to the olfactory receptor OLFR734, a member of the GPCR family located on the hepatocyte membrane, where it exerts glycogenic effects. Activation of OLFR734 leads to PKA activation, which stimulates hepatic gluconeogenesis and increases circulating glucose levels (Figure 5). Asprosin also activates orexigenic neurons to enhance appetite and regulate energy stores. However, in orexigenic neurons, asprosin regulates appetite by binding to receptor-type tyrosine-protein phosphatase delta (Ptprd) located on AgRP neurons.[37]

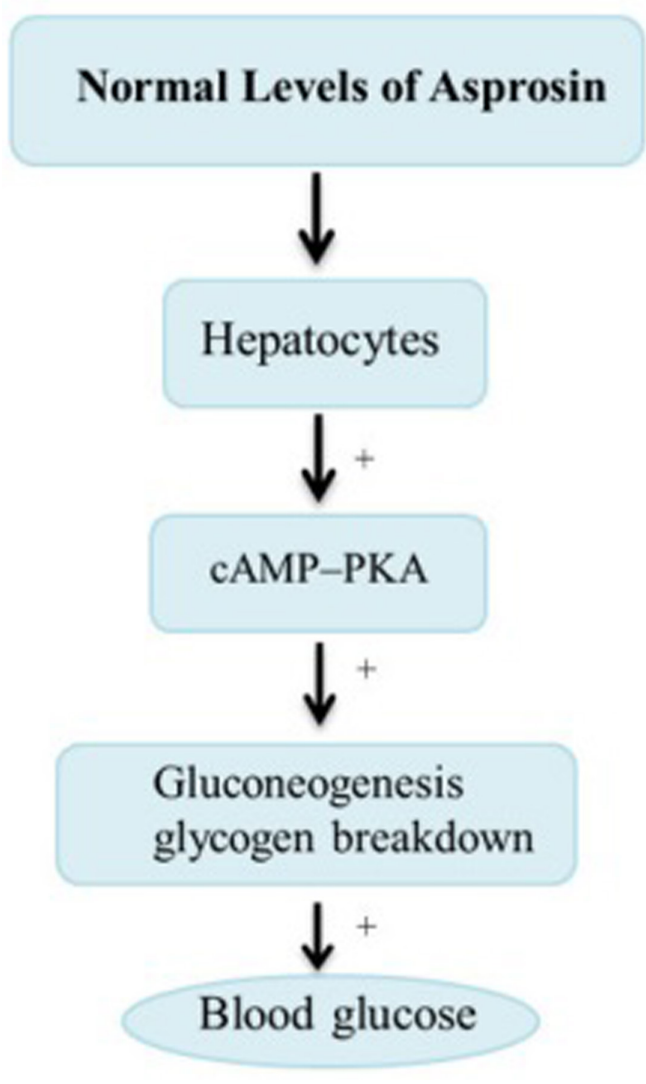

Figure 5. Physiological functions of asprosin at normal levels. cAMP/PKA, cyclic AMP/protein kinase A.

C1q Tumor Necrosis Factor–Related Proteins

C1q tumor necrosis factor–related proteins (CTRPs) are numbered from 1 to 15 based on their structural differences. They are highly conserved proteins and considered homologs of ApN.[38] Except for CTRP4, all CTRPs are secreted proteins composed of 3 main domains: an N-terminal domain with conserved cysteine residues and a variable region, a collagen-like domain, and a C-terminal globular C1q (gC1q) domain, which forms a trimeric structure resembling the subunit structure of complement protein C1q. The CTRP4 differs from the others in that it lacks a collagen domain and instead contains a second C1q domain. The CTRP15, on the other hand, contains a shorter collagen domain.[38-40]

Similar to ApN, CTRPs exert metabolic activity by binding to AdipoR1 and AdipoR2 receptors.[40] The CTRPs are synthesized in peripheral tissues such as adipose tissue, liver, skeletal muscle, and cardiac muscle in both rodents and humans. The CTRP signaling pathways enhance AMPK, PI3K/Akt, and MAPK/ERK activation, while suppressing inflammation-related NF-κB and toll-like receptor (TLR) pathways.[38-40]

Resistin

Resistin, which contains a high amount of cysteine amino acids in its structure, exhibits pro-inflammatory effects in pathological conditions such as obesity, T2DM, chronic inflammation, metabolic syndrome, infectious diseases, and cancer. Resistin, considered a component of the immune and defense system, is a small endogenous peptide localized in the epithelial barrier and leukocytes. Resistin belongs to the resistin-like molecule hormone family.

Resistin is produced by the Retn gene in humans and mice. In humans, resistin is synthesized by adipocytes, immune cells, macrophages, monocytes, and neutrophils. Resistin exerts its effects by binding to adenylyl cyclase-associated protein 1 (CAP1), TLR4, an isoform of decorin (ΔDCN), and receptor tyrosine kinase-like orphan receptor 1 (ROR1). By binding to the CAP1 receptor, resistin induces the activation of cAMP-dependent protein kinase A and increases the synthesis of NF-κB-mediated inflammatory cytokines (IL-6, TNF-α, and IL-1β). Resistin enhances STAT3 activation. The interaction between resistin and TLR4 activates the c-Jun N-terminal kinase (JNK) and p38 pathways. Resistin interacts with the ROR1 receptor and induces the activation of ERK1/2 in 3T3-L1 preadipocytes.[41]

Dysregulation of Novel Adipokines in Metabolic Disorders

Acylation-Stimulating Protein

Acylation-stimulating protein (ASP) enhances TG synthesis within adipose tissue. Its excessive production promotes abnormal TG accumulation in adipose depots, thereby contributing to the pathogenesis of obesity. While ASP facilitates cellular glucose uptake, chronically elevated ASP levels are associated with insulin resistance, ultimately leading to the development of T2DM. Moreover, dysregulated ASP expression supports the progression of pathological conditions such as dyslipidemia, cardiovascular diseases, and metabolic syndrome.[36]

Asprosin

It was first identified in patients with neonatal progeroid syndrome (NPS), a condition characterized by extreme leanness,

reduced appetite and energy expenditure, and lipodystrophy in the face and limbs. In NPS, a 3′ splice-site mutation occurs in the fibrillin-1 (FBN1) gene. This mutation occurs within the last 50 nucleotides of the penultimate exon, resulting in a mutant profibrillin that fails to produce functional asprosin, thereby leading to low asprosin levels. Asprosin expression increases in WAT during fasting. Asprosin regulates physiological processes such as appetite control, glycolysis, insulin resistance, and apoptosis in both the central nervous system and peripheral tissues.

However, excessive secretion of asprosin has been associated with pancreatic β-cell dysfunction and induction of apoptosis. In muscle tissue, asprosin also exerts pro-inflammatory effects, contributing to insulin resistance. Asprosin levels are increased in pathological conditions such as obesity, T2DM, polycystic ovary syndrome (PCOS), non-alcoholic fatty liver disease (NAFLD), and cardiovascular disease. Moreover, increased asprosin concentration suppresses POMC neurons while activating AgRP neurons in the hypothalamus, which promotes the development of obesity due to excessive appetite. In muscle and adipose tissues, it leads to the development of insulin resistance, resulting in T2DM. In the immune system, it stimulates the synthesis of pro-inflammatory cytokines (Figure 6).[37]

C1q Tumor Necrosis Factor–Related Proteins

In metabolic tissues, CTRPs regulate insulin sensitivity and fatty acid oxidation. Additionally, they play roles in modulating inflammation and glucose metabolism in endothelial cells. Dysfunction in CTRPs can contribute to endothelial cell impairment, foam cell formation, and enhanced vascular smooth muscle cell migration, all of which are associated with the development of cardiovascular diseases. Moreover, metabolic disorders such as obesity, insulin resistance, T2DM, NAFLD, and PCOS are linked to altered CTRP function.[40] Studies have shown elevated CTRP9 levels in the blood of diabetic and ischemia/reperfusion (I/R) injury model mice.[42]In patients with coronary artery disease, serum CTRP3 levels are decreased, while CTRP1 levels show a positive correlation with serum lipid levels.[40] CTRP2, CTRP3, CTRP12, and CTRP15 concentrations are increased in MI or I/R injury (Figure 7).[39]

Resistin

In cancer cells, resistin and its receptors exhibit uncontrolled proliferation. In pancreatic cancers, CAP1 expression is increased, whereas in tumor tissues, TLR4 expression is elevated.[43] Furthermore, elevated levels of resistin or its receptors contribute to the development of pathological conditions such as insulin

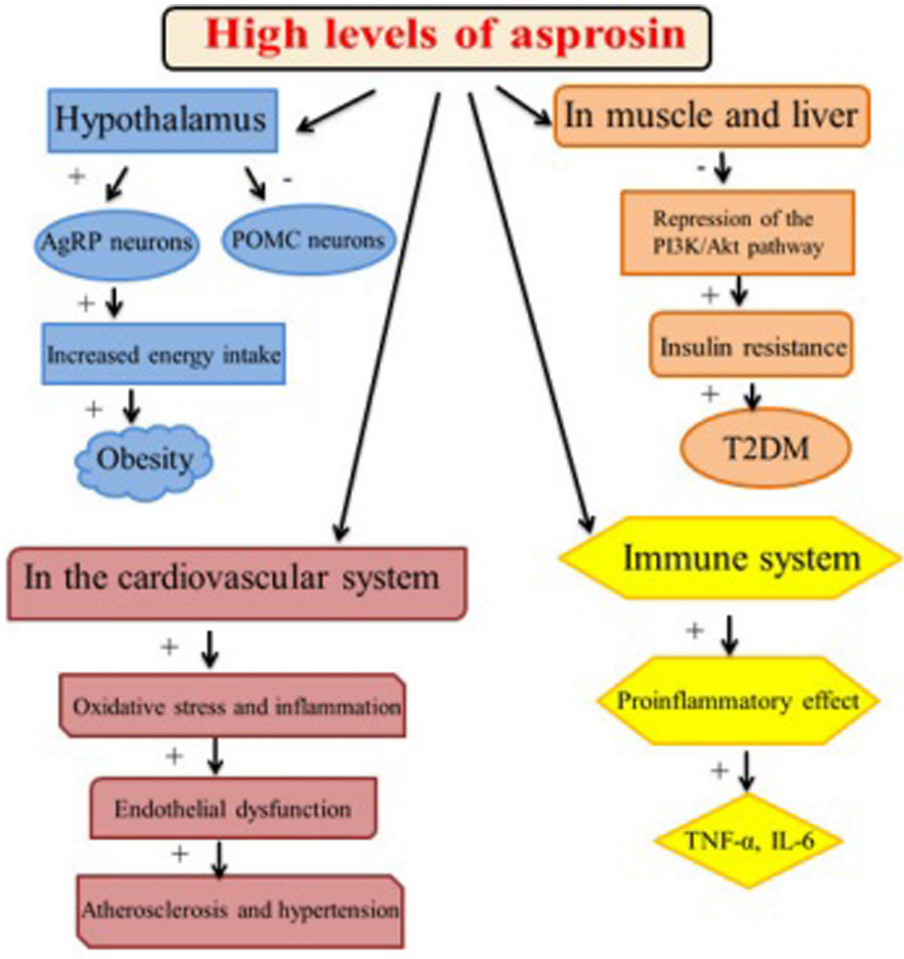

Figure 6. The effects of asprosin vary according to ıts circulating concentration levels. AgRP, agouti-related peptide; α-MSH, α-melanocyte-stimulating hormone; CART, cocaine- and amphetamine-regulated transcript; IL-6, interleukin-6; PI3K/Akt, phosphoinositide 3-kinase / protein kinase B; POMC, proopiomelanocortin; TNF-α, tumor necrosis factor-alpha; T2DM, type 2 diabetes mellitus.

CTRP Members	Main Function	Pathways It Activates	Pathophysiological conditions
CTRP1	Fatty acid oxidation, energy expenditure	AMPK, ACC	Obesity, hyperlipidemia
CTRP2	Metabolic regulation, insulin sensitivity	AMPK, PI3K/Akt	Myocardial infarction, I/R, metabolic disorders
CTRP3	Anti-inflammatory, hepatoprotective	PI3K/Akt, NF-κB inhibition	NAFLD, T2D, cardiovascular disease
CTRP4	Appetite suppression, energy balance	Hypothalamic NPY/AgRP Regulation: STAT3	Obesity
CTRP5	Glucose uptake, insulin sensitivity	AMPK, GLUT4 activation	T2DM
CTRP6	Inflammation control, glucose metabolism	AMPK, GLUT4 activation	PCOS, inflammation
CTRP9	Cardiovascular protection, insulin sensitivity	AMPK, Akt, MAPK	T2D, I/R, cardiovascular disease
CTRP12	Anti-inflammatory, hepatic lipid metabolism	AMPK, NF-κB inhibition	I/R, PCOS
CTRP13	Appetite suppression, energy expenditure	Hypothalamic NPY/AgRP regulation	Obesity
CTRP15	Metabolic regulation, cardioprotective	AMPK, S1P/cAMP/Akt	Myocardial infarction, I/R

Figure 7. Main functions of CTRPs, signaling pathways and their effects in pathophysiology. AMPK, 5′-AMP-activated protein kinase; ACC, acetyl-CoA carboxylase; AgRP, agouti-related peptide; Akt, protein kinase B; CTRP, C1q tumor necrosis factor (TNF)-related proteins; GLUT, glucose transporters; I/R, ischemia/reperfusion; MAPK, mitogen-activated protein kinase; NPY, neuropeptide Y; NAFLD, non-alcoholic fatty liver disease; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K/Akt, phosphoinositide 3-kinase / protein kinase B; PCOS, polycystic ovary syndrome; S1P, sphingosine-1-phosphate; STAT, signal transducer and activator of transcription proteins; T2DM, type 2 diabetes mellitus.

resistance, inflammation, obesity, cardiovascular diseases, metabolic syndrome, certain cancers, and autoimmune disorders.[41]

Therapeutic Implications and Future Perspectives of Novel Adipokines

Acylation Stimulating Protein

Acylation stimulating protein plays a significant regulatory role in lipid biosynthesis and TG storage. In humans, ASP predominantly stimulates TG synthesis in mature adipocytes and to a lesser extent in preadipocytes. In 1 study, mice fed a high-fat diet (HFD) were treated with antibodies against ASP (Anti-ASP) and human recombinant ASP (rASP). It was demonstrated that rASP enhanced fatty acid uptake in adipocytes, whereas treatment with Anti-ASP led to an increase in energy expenditure in the mice.[44] The C5L2 signaling pathway activates diacylglycerol acyltransferase, a key enzyme for TG synthesis, thereby promoting fatty acid esterification. ASP also enhances glucose transport in adipocytes, smooth muscle cells, preadipocytes, and fibroblasts by stimulating GLUT1, GLUT3, and GLUT4 transporters. In a study, ASP/C5L2-neutralizing antibodies were developed and utilized to block the interaction between ASP and its receptor C5L2. Mice administered these ASP/C5L2-neutralizing antibodies exhibited delayed postprandial TG and free fatty acid clearance.[45]

Asprosin

In anorexigenic neurons of the brain, asprosin inhibits POMC production. In the liver, it stimulates glycogenolysis by promoting the breakdown of glycogen protein, thereby increasing glucose release into the bloodstream. In peripheral tissues, asprosin also promotes skeletal muscle development. In a study on rats, asprosin administration was shown to stimulate the synthesis of luteinizing hormone, follicle-stimulating hormone, and testosterone via activation of the hypothalamic-pituitary axis.[46] The effects of asprosin and its receptors on metabolism and hormones could be further investigated in future studies, which may provide valuable insights into their potential therapeutic roles.[37]

C1q Tumor Necrosis Factor–Related Proteins

Under physiological conditions, CTRPs play important roles in maintaining body homeostasis. Transgenic mice overexpressing CTRP1 and fed a HFD exhibit resistance to obesity and have lower body weight compared to control mice. CTRP1 enhances fatty acid oxidation and energy expenditure, thereby reducing overall fat mass. In 1 study, the therapeutic effects and underlying mechanisms of CTRP1 on DIO, T2DM, and fatty liver disease were investigated. It was demonstrated that hydrodynamic gene delivery of CTRP1 improved metabolic homeostasis in obese and diabetic mice, suppressed HFD-induced weight gain and hepatic steatosis, and reduced insulin resistance.[40] The CTRPs synthesized in the hypothalamus—such as CTRP4, CTRP9, and CTRP13—are involved in the regulation of appetite and body weight.[39] In a study on HFD-fed mice, CTRP4 was shown to suppress appetite by downregulating orexigenic NPs such as NPY and AgRP.[38] In a study, CTRP9 was administered to HFD-fed mice, and it was observed that MI was reduced and cardiac functional

Table 4. Overview of Other Novel Adipokines: Biochemical Characteristics and Physiological–Pathophysiological Roles, and Therapeutic Effects

Adipokine	Sites of Synthesis	Receptors	Signaling Pathway	Physiological Roles	Pathophysiological Roles	Therapeutic Effect
Subfatin (METRNL)	Adipose tissue, skeletal muscle, CNS	KIT	JAK/ STAT3/6 AMPK PPAR-γ p38 MAPK cAMP/ PKA/ SIRT1	It regulates WAT-to-BAT conversion It shows protective effects in diseases accompanied by chronic inflammation, regulates metabolism, enhances insulin action, CVD, reduces muscle damage, and promotes muscle regeneration It exerts neuroprotective and antioxidant effects	Obesity Metabolic syndrome Inflammation T2DM CVD PCOS COPD Neurological disorders[51]	–
Irisin	Muscle, adipose tissue, pancreas, salivary glands, peripheral tissues	Integrins (α1β1 and αVβ5)	p38 MAPK/ ERK1/2 AMPK PI3K/Akt cAMP/ PKA/ CREB	Promotes WAT-to-BAT conversion It reduces the risk of developing metabolic diseases, exerts protective effects against CVD, increases muscle mass and endurance, and possesses neuroprotective effects, osteoblast differentiation It exerts anti-inflammatory and antioxidant effects	Obesity Metabolic syndrome[52]	–
Isthmin-1 (ISM1)	Cerebellum, cerebral cortex, hippocampuseye, kidney, skeletal muscle, heart, lungs	αvβ5 Integrin α8β1 GRP78	p38 MAPK/ ERK1/2 AMPK PI3K/Akt TBK1–IRF3–IFN	It regulates metabolic homeostasis, prevents insulin resistance, exerts antiviral effects against viral infections, induces apoptosis, promotes endothelial permeability, and is involved in physiogenesis	T2DM	Since it possesses antiviral activity, studies on ISM1 signaling pathways are ongoing Therapeutic agents have begun to be developed because it induces apoptosis in mitochondrial dysfunction via the αvβ5 receptor[53]
Vaspin (serpin derived from visceral fat tissue (SERPINA 12)	Adipocyte cells from liver, muscle, pancreas, and peripheral tissues	INSR IGF-1R GRP78 LRP1	Akt AMPK STAT3 MAPK/ p38 MAPK/ ERK	It increases endothelial nitric oxide synthase activity It has negative effect on NFκB It exerts anti-apoptotic effects in endothelial cell Increases POMC synthesis It increases insulin sensitivity and suppresses the excessive secretion of adipokines such as TNF-α, leptin, and resistin by showing anti-inflammatory effects[54] It supports chondrogenic and osteoblastic cell survival and has been shown to attenuate RANKL-induced osteoclastoge-nesis[4] Regulates the proliferation and steroidogenesis of ovarian follicle cells	Metabolic syndrome Insulin resistance Impaired osteoblast/osteoclast balance Inflammation CVD	It is being investigated as a potential therapeutic agent for pathological conditions such as GDM, PCOS, MetS, hypothyroidism, and hyperthyroidism[54]

(*Continued*)

Table 4. Overview of Other Novel Adipokines: Biochemical Characteristics and Physiological–Pathophysiological Roles, and Therapeutic Effects (Continued)

Nesfatin-1 (NESF)	Hypothalamus and peripheral tissues	GPCRs	cAMP PKA AMPK ERK/ MAPK Akt NO-cGMP system	It suppresses appetite. Regulates homeostasis of metabolism. Increases insulin sensitivity. Activates ion channels. Regulates blood pressure. Provides protection against ischemic/ perfusion. Protection against neurological diseases.	Obesity T2DM CVD Metabolic syndrome Neurological disorders Elevated in OA and induces COX-2, IL-6, IL-8 and other pro-inflammatory mediators in human chondrocytes, thereby contributing to cartilage inflammation and degradation.	The incomplete identification of its specific receptors currently limits the therapeutic application of nesfatin-1 as a potential therapeutic agent[55]
Chemerin	Adipose tissue, liver, skin, lung, pancreas, and kidney	CMKLR1 GPR1 CCRL2	MAPK/ ERK1/2 PI3K/Akt AMPK NF-κB	Regulates metabolic hematostasis and immunity Controls appetite in the brain	Pro-inflammatory effect Metabolic syndrome Obesity CVD Cancer	Chemerin agonists or antagonists are being used for metabolic and inflammatory diseases Chemerin receptor blockade (CMKLR1 antagonists) improved bone mass in db/db mice[4,56]

AMPK, 5′ adenosine monophosphate-activated protein kinase; BAT, brown adipose tissue; CAP1, cyclase-associated actin cytoskeleton regulatory protein 1; C5L2, ASP receptor; CCRL2, C-C motif chemokine receptor-like 2; cAMP/PKA, cyclic AMP/protein kinase A; cGMP, cyclic guanosine monophosphate; COX-2, cyclooxygenase-2; COPD, chronic obstructive pulmonary diseases; CREB, cyclic AMP regulatory element-binding protein; CMKLR1, chemokine-like receptor 1; cPLA2, phospholipase A2; CNS, central nervous system; CVD, Cardiovascular diseases; ERK, extracellular signal-regulated kinase; GDM, gestational diabetes mellitus; GLUT, glucose transporter; GPR1, G protein-coupled receptor 1; GRP78, glucose-regulated protein 78; IGF-1R, insulin-like growth factor-1 receptor; INSR, insulin receptor; IRS, insulin receptor substrate; IRF3, interferon regulatory factor 3; IFN, interferon; JAK/STAT, Janus kinases/signal transducer and activator of transcription proteins; KIT, (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) receptor tyrosine kinas; LepR, leptin receptor; LRP1, Low-density Lipoprotein Receptor-Related Protein 1; MAP3K1, mitogen-activated protein kinase kinase kinase 1; MetS, metabolic syndrome; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; METRNL, meteorin-like protein; MSC, mesenchymal stem cell; NO, nitric oxide; p38 MAPK, p38 mitogen-activated protein kinase; PCOS, polycystic ovary syndrome; PI3K/Akt, phosphoinositide 3-kinase / protein kinase B; PKC, protein kinase C; PPAR-γ, peroxisome proliferator-activated receptor gamma; RANK, receptor activator of NF-κB; SERPINA 12, serpin derived from visceral fat tissue; TAG, triglyceride; TBK1, TANK-binding kinase 1; TLR, toll-like receptor; T2DM, type 2 diabetes mellitus; WAT, white adipose tissue.

improvement occurred in these mice.[42] Similarly, administration of CTRP13 suppressed appetite and resulted in weight loss. In 1 study, intracerebroventricular administration of recombinant CTRP13 in mice was shown to reduce food intake and induce weight loss.[47]In skeletal muscle, CTRPs promote fatty acid oxidation and enhance insulin sensitivity. CTRP1, in skeletal muscle, increases fatty acid oxidation and energy expenditure through the activation of ACC and AMPK.[40] In myocytes, CTRP5 and CTRP6 activate AMPK, leading to stimulation of GLUT4 transporters and increased glucose uptake.[39] A study, administration of CTRP12 to genetically (ob/ob) and DIO mice was shown to improve insulin sensitivity and, in part, enhance insulin signaling in adipose tissue and liver. Additionally, CTRP12 was reported to suppress gluconeogenesis in hepatocytes and increase glucose uptake in adipocytes by activating the PI3K-Akt signaling pathway independently of insulin.[48] The CTRP9 also enhances insulin sensitivity in myocytes by activating the p44/42 MAPK, Akt, and AMPK signaling pathways (Figure 6).[39,40]

Resistin

The development of therapeutic resistance in cancer treatment is a critical issue. Resistin, through DNA methyltransferases (DNMT1 and DNMT3) and epigenetic therapy, has been shown to increase the expression of ATP-binding cassette (ABC) transporters in myeloma. The overexpression of ABC transporters induces intrinsic or acquired drug resistance in various cancers.[49]Furthermore, resistin has been shown to increase the levels of fatty acid synthase, caveolin-1, and P-glycoprotein in melanoma resistant to dacarbazine (DTIC) treatment.[50]Resistin inhibitors are used for insulin resistance, T2DM, and cardiovascular diseases. In the treatment of conditions such as dyslipidemia and hypertension, the reduction of resistin levels is planned.[41]

Other Novel Adipokines

The structures, tissues of synthesis, receptors, signaling pathways, pathological and pathophysiological roles, and therapeutic effects of other novel adipokines are presented in Table 4.

Adipokines are protein-based substances secreted not only by adipose tissue but also by various other tissues, possessing a wide range of biological functions. Since the dysregulation of these molecules plays a role in the development of various diseases, elucidating the underlying mechanisms and developing targeted therapeutic strategies may provide significant therapeutic approaches for combating these diseases in the future.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.N.Ş., M.Y.A., S.K., K.Y., S.A.; Design – E.N.Ş., M.Y.A., S.K., K.Y., S.A.; Supervision – E.N.Ş., M.Y.A., S.K., K.Y., S.A.; Resources – E.N.Ş., M.Y.A., S.K., K.Y., S.A.; Materials – E.N.Ş., M.Y.A., S.K., K.Y., S.A.; Data Collection and/or Processing – E.N.Ş., M.Y.A., S.K., K.Y., S.A.; Analysis and/or Interpretation – E.N.Ş., M.Y.A., S.K., K.Y., S.A.; Literature Search – E.N.Ş., M.Y.A., S.K., K.Y., S.A.; Writing Manuscript – E.N.Ş., M.Y.A., S.K., K.Y., S.A.; Critical Review – E.N.Ş., M.Y.A., S.K., K.Y., S.A.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

References

1. He N, Liu M, Wu Y. Adipose tissue and hematopoiesis: friend or foe? *J Clin Lab Anal*. 2023;37(6):e24872. [CrossRef]
2. Richard AJ, White U, Elks CM, et al. Adipose tissue: physiology to metabolic dysfunction. *MDText.com*, Inc. In: Feingold KR, Ahmed SF, Anawalt B, et al., eds.; 2000-.updated 2020 April 4. Endotext [Internet]. South Dartmouth (MA). https://www.ncbi.nlm.nih.gov/books/NBK555602.
3. Khan M, Joseph F. Adipose tissue and adipokines: the association with and application of adipokines in obesity. *Scientifica*. 2014;2014:328592. [CrossRef]
4. Farrag Y, Farrag M, Varela-García M, et.al. Adipokines as potential pharmacological targets for immune inflammatory rheumatic diseases: focus on rheumatoid arthritis, osteoarthritis, and intervertebral disc degeneration. *Pharmacol Res*. 2024;205:107219. [CrossRef]
5. Mantzoros CS, Magkos F, Brinkoetter M, et.al. Leptin in human physiology and pathophysiology. *Am J Physiol Endocrinol Metab*. 2011;301(4):E567-E584. [CrossRef]
6. Park HK, Ahima RS. Leptin signaling [rep.]. *F1000Prime Rep*. 2014;6:73. [CrossRef]
7. Obradovic M, Sudar-Milovanovic E, Soskic S, et.al. Leptin and obesity: role and clinical ımplication. *Front Endocrinol*. 2021;12:585887. [CrossRef]
8. Nguyen TMD. Adiponectin: role in physiology and pathophysiology. *Int J Prev Med*. 2020;11:136. [CrossRef]
9. Fisman EZ, Tenenbaum A. Adiponectin: a manifold therapeutic target for metabolic syndrome, diabetes, and coronary disease? *Cardiovasc Diabetol*. 2014;13:103. [CrossRef]
10. Murali S, Aradhyam GK. Structure–function relationship and physiological role of apelin and its G protein coupled receptor. *Biophys Rev*. 2023;15(1):127-143. [CrossRef]
11. Villano I, La Marra M, Di Maio G, et al. Physiological role of orexinergic system for health. *Int J Environ Res Public Health*. 2022;19(14):8353. [CrossRef]
12. Halverson SJ, Warhoover T, Mencio GA, Lovejoy SA, Martus JE, Schoenecker JG. Leptin elevation as a risk factor for slipped capital femoral epiphysis independent of obesity status. *J Bone Joint Surg Am*. 2017;99(10):865-872. [CrossRef]
13. Ye H, Cao T, Shu Q, et.al. Blockade of orexin receptor 1 attenuates morphine protracted abstinence-induced anxiety-like behaviors in male mice. *Psychoneuroendocrinology*. 2023;151:106080. [CrossRef]
14. Moon H-S, Matarese G, Brennan AM, et al. Efficacy of Metreleptin in obese patients with type 2 diabetes: cellular and molecular pathways underlying leptin tolerance. *Diabetes*. 2011;60(6):1647-1656. [CrossRef]
15. Hukshorn CJ, Westerterp-Plantenga MS, Saris WHM. Pegylated human recombinant leptin (PEG-OB) causes additional weight loss in severely energy-restricted, overweight men. *Am J Clin Nutr*. 2003;77(4):771-776. [CrossRef]
16. Trevaskis JL, Lei C, Koda JE, Weyer C, Parkes DG, Roth JD. Interaction of leptin and amylin in the long-term maintenance of weight loss in diet-induced obese rats. *Obesity (Silver Spring)*. 2009;18(1):21-26. [CrossRef]
17. Cornish J, Callon KE, Bava U, et.al. Leptin directly regulates bone cell function in vitro and reduces bone fragility in vivo. *J Endocrinol*. 2002;175(2):405-415. [CrossRef]
18. Foo J-P, Polyzos SA, Anastasilakis AD, Chou S, Mantzoros CS. The effect of leptin replacement on parathyroid hormone, RANKL-osteoprotegerin axis, and wnt inhibitors in young women with hypothalamic amenorrhea. *J Clin Endocrinol Metab*. 2014;99(11):E2252-E2258. [CrossRef]
19. Liu Y, Turdi S, Park T, et.al. Adiponectin corrects high-fat diet–ınduced disturbances in muscle metabolomic profile and whole-body glucose homeostasis. *Diabetes*. 2013;62(3):743-752. [CrossRef]
20. Rzepka-Górska I, Bedner R, Cymbaluk-Płoska A, Chudecka-Głaz A. Serum adiponectin in relation to endometrial cancer and endometrial hyperplasia with atypia in obese women. *Eur J Gynaecol Oncol*. 2008;29(6):594-597. [CrossRef]
21. Jiang J, Fan Y, Zhang W, et.al. Adiponectin suppresses human pancreatic cancer growth through attenuating the β-catenin signaling pathway. *Int J Biol Sci*. 2019;15(2):253-264. [CrossRef]
22. Yang J, Park OJ, Kim J, et al. Adiponectin deficiency triggers bone loss by up-regulation of osteoclastogenesis and down-regulation of osteoblastogenesis. *Front Endocrinol (Lausanne)*. 2019;10:815. [CrossRef]

23. Stojanovic SS, Arsenijevic NA, Djukic A, et al. Adiponectin as a potential biomarker of low bone mineral density in postmenopausal women with metabolic syndrome. Acta Endocrinol (Buchar). 2018;14(2):201-207. [CrossRef]
24. Yang P, Read C, Kuc RE, et al. A novel cyclic biased agonist of the apelin receptor, MM07, is disease modifying in the rat monocrotaline model of pulmonary arterial hypertension. *Br J Pharmacol*. 2019;176(9):1206-1221. [CrossRef]
25. Girault-Sotias P-E, Deloux R, De Mota ND, et al. The metabolically resistant apelin-17 analogue LIT01-196 reduces cardiac dysfunction and remodelling in heart failure after myocardial infarction. *Can J Cardiol*. 2025;41(5):911-924. [CrossRef]
26. Li Z, Zhao Q, Zhou J, Li Y, Zheng Y, Chen L. A reactive oxygen species-responsive hydrogel loaded with Apelin-13 promotes the repair of spinal cord injury by regulating macrophage M1/M2 polarization and neuroinflammation. *J Nanobiotechnology*. 2025;23(1):12. [CrossRef]
27. Li M, Fang H, Hu J. Apelin-13 ameliorates metabolic and cardiovascular disorders in a rat model of type 2 diabetes with a high-fat diet. *Mol Med Rep*. 2018;18(6):5784-5790. [CrossRef]
28. Rodgers RJ, Halford JCG, Nunes de Souza RL, et.al. SB-334867, a selective orexin-1 receptor antagonist, enhances behavioural satiety and blocks the hyperphagic effect of orexin-A in rats. *Eur J Neurosci*. 2001;13(7):1444-1452. [CrossRef]
29. Ishikawa T, Kurimoto E, Joyal AA, Koike T, Kimura H, Scammell TE. An orexin agonist promotes wakefulness and inhibits cataplexy through distinct brain regions. *Curr Biol*. 2025;35(9):2088-2099.e4. [CrossRef]
30. Amaral IM, Ouaidat S, Scheffauer L, et.al. Exploring the role of orexins in the modulation of social reward. *Psychopharmacol (Berl)*. 2025;242(2):401-412. [CrossRef]
31. Gough P, Myles IA. Tumor necrosis factor receptors: pleiotropic signaling complexes and their differential effects. *Front Immunol*. 2020;11:585880. [CrossRef]
32. Han MS, White A, Perry RJ, et al. Regulation of adipose tissue inflammation by interleukin 6. *Proc Natl Acad Sci U S A*. 2020;117(6):2751-2760. [CrossRef]
33. Al-Mansoori L, Al-Jaber H, Prince MS, Elrayess MA. Role of inflammatory cytokines, growth factors and adipokines in adipogenesis and insulin resistance. *Inflammation*. 2022;45(1):31-44. [CrossRef]
34. Carlini V, Noonan DM, Abdalalem E, et.al. The multifaceted nature of IL-10: regulation, role in immunological homeostasis and its relevance to cancer, COVID-19 and post-COVID conditions. *Front Immunol*. 2023;14:1161067. [CrossRef]
35. Dakroub A, A Nasser SA, Younis N, et.al. Visfatin: A possible role in cardiovasculo-metabolic disorders. *Cells*. 2020;9(11):2444. [CrossRef]
36. Maslowska M, Legakis H, Assadi F, Cianflone K. Targeting the signaling pathway of acylation stimulating protein. *J Lipid Res*. 2006;47(3):643-652. [CrossRef]
37. Farrag M, Ait Eldjoudi DA, Gonzalez-Rodrıguez M, et al. Asprosin in health and disease, a new glucose sensor with central and peripheral metabolic effects. *Front Endocrinol (Lausanne)*. 2023;13:1101091. [CrossRef]
38. Ye L, Jia G, Li Y, et.al. C1q/TNF-related protein 4 restores leptin sensitivity by downregulating NF-κB signaling and microglial activation. *J Neuroinflammation*. 2021;18(1):159. [CrossRef]
39. Ramanjaneya M, Jerobin J, Bettahi I, Siveen KS, Abou-Samra AB. Emerging roles of C1Q tumor necrosis factor-related proteins in metabolic diseases. *Transl Med Commun*. 2021;6(1):5. [CrossRef]
40. Ren M, Pan J, Yu X, Chang K, Yuan X, Zhang C. CTRP1 prevents high fat diet-induced obesity and improves glucose homeostasis in obese and STZ-induced diabetic mice. *J Transl Med*. 2022;20(1):449. [CrossRef]
41. Sudan SK, Deshmukh SK, Poosarla T, et.al. Resistin: an inflammatory cytokine with multi-faceted roles in cancer. *Biochim Biophys Acta Rev Cancer*. 2020;1874(2):188419. [CrossRef]
42. Su H, Yuan Y, Wang X-M, et.al. Inhibition of CTRP9, a novel and cardiac-abundantly expressed cell survival molecule, by TNFα-initiated oxidative signaling contributes to exacerbated cardiac injury in diabetic mice. *Basic Res Cardiol*. 2013;108(1):315. [CrossRef]
43. Zhang M, Yan L, Wang G-J, Jin R. Resistin effects on pancreatic cancer progression and chemoresistance are mediated through its receptors CAP1 and TLR4. *J Cell Physiol*. 2019;234(6):9457-9466. [CrossRef]
44. Paglialunga S, Fisette A, Munkonda M, Gao Y, Richard D, Cianflone K. The effects of acylation stimulating protein supplementation vs antibody neutralization on energy expenditure in wildtype mice. *BMC Physiol*. 2010;10:4. [CrossRef]
45. Cui W, Paglialunga S, Kalant D, et.al. Acylation-stimulating protein/C5L2-neutralizing antibodies alter triglyceride metabolism in vitro and in vivo. *Am J Physiol Endocrinol Metab*. 2007;293(6):E1482-E1491. [CrossRef]
46. Keskin T, Erden Y, Tekin S. Intracerebroventricular asprosin administration strongly stimulates hypothalamic-pituitary-testicular axis in rats. *Mol Cell Endocrinol*. 2021;538:111451. [CrossRef]
47. Byerly MS, Swanson R, Wei Z, Seldin MM, McCulloh PS, Wong GW. A central role for C1q/TNF-related protein 13 (CTRP13) in modulating food intake and body weight. *PLOS One*. 2013;8(4):e62862. [CrossRef]
48. Wei Z, Peterson JM, Lei X, et.al. C1q/TNF-related protein-12 (CTRP12), a novel adipokine that improves insulin sensitivity and glycemic control in mouse models of obesity and diabetes. *J Biol Chem*. 2012;287(13):10301-10315. [CrossRef]
49. Pang J, Shi Q, Liu Z, et.al. Resistin induces multidrug resistance in myeloma by inhibiting cell death and upregulating ABC transporter expression. *Haematologica*. 2017;102(7):1273-1280. [CrossRef]
50. Malvi P, Chaube B, Singh SV, et.al. Elevated circulatory levels of leptin and resistin impair therapeutic efficacy of dacarbazine in melanoma under obese state. *Cancer Metab*. 2018;6:2. [CrossRef]
51. Li Z, Gao Z, Sun T, et.al. Meteorin-like/Metrnl, a novel secreted protein implicated in inflammation, immunology, and metabolism: a comprehensive review of preclinical and clinical studies. *Front Immunol*. 2023;14:1098570. [CrossRef]
52. Waseem R, Shamsi A, Mohammad T, et al. FNDC5/Irisin: physiology and pathophysiology. *Molecules*. 2022;27(3):1118. [CrossRef]
53. Hu M, Zhang X, Hu C, Teng T, Tang QZ. A brief overview about the adipokine: Isthmin-1. *Front Cardiovasc Med*. 2022;9:939757. [CrossRef]
54. Kurowska P, Mlyczyńska E, Dawid M, et.al. Review: vaspin (SERPINA12) expression and function in endocrine cells. *Cells*. 2021;10(7):1710. [CrossRef]
55. Damian-Buda A-C, Matei DM, Ciobanu L, et.al. Nesfatin-1: A novel diagnostic and prognostic biomarker in digestive diseases. *Biomedicines*. 2024;12(8):1913. [CrossRef]
56. Mitsis A, Khattab E, Myrianthefs M, et.al. Chemerin in the spotlight: revealing its multifaceted role in acute myocardial infarction. *Biomedicines*. 2024;12(9):2133. [CrossRef]