Review

Secretion Patterns of Leptin: A Key Component in the Regulation of Energy Homeostasis and Its Therapeutic Applications

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Review

Secretion Patterns of Leptin: A Key Component in the Regulation of Energy Homeostasis and Its Therapeutic Applications

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Abstract

Leptin is the oldest studied adipokine, and its mechanism of action in the regulation of energy metabolism remains a hot topic of current research. In this paper, we systematically review the progress of clinical and basic research on leptin and energy metabolism from 1994 to 2025. It is shown that leptin can regulate the energy metabolism homeostasis through autocrine, paracrine and neurohumoral pathways (e.g., hypothalamic-leptin-melanocortin axis). In addition, the effects of mainstream weight loss strategies such as dietary control, pharmacological interventions and exercise on leptin levels and their underlying mechanisms were investigated in this paper, with the aim of providing a theoretical basis for the clinical application of leptin in metabolic diseases (e.g., obesity, diabetes mellitus). Future studies need to further clarify the molecular mechanisms of leptin resistance and explore precise intervention strategies based on the leptin signaling pathway.

Keywords: leptin; energy metabolism; obesity; endocrine regulation

1. Introduction

Energy homeostasis is the state in which an organism maintains a long-term dynamic equilibrium between energy intake and energy expenditure through a series of physiological regulatory mechanisms. It is a core physiological process for the maintenance of life and health. It is not a simple static equilibrium, but rather a dynamic, finely regulated process. Governed by the central nervous system (particularly the hypothalamus), it involves a complex network of communication between multiple organs and numerous signalling molecules. Its purpose is to coordinate energy intake, expenditure and storage in order to maintain long-term stability in body weight and metabolism.Understanding energy homeostasis is crucial for elucidating the pathogenesis of metabolic diseases such as obesity and diabetes, and for developing strategies for their prevention and treatment. Among these, leptin—the 'satiety signal' produced by adipose tissue—is a key regulatory molecule involved in maintaining energy homeostasis.

Leptin, the best-known adipokine, has been the subject of extensive research since its discovery in 1994. It has been found that leptin plays a role in energy metabolism by suppressing appetite, increasing energy expenditure and maintaining insulin sensitivity[1,2]. Research indicates that leptin acts as a homeostatic signal (a fat signal) that regulates body weight; for example, mice lacking the leptin gene (ob/ob mice) and humans with congenital leptin deficiency caused by rare genetic mutations in the leptin gene become severely obese[3–5]. However, administering leptin to ob/ob mice reduces food intake and increases energy expenditure, leading to an energy deficit and weight loss. Furthermore, leptin monotherapy in obese individuals with congenital leptin deficiency can also result in sustained weight loss.

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Furthermore, leptin is a cytokine secreted primarily by white adipose tissue in proportion to fat mass; consequently, leptin levels reflect the body's fat stores. In terms of energy metabolism, leptin binds to leptin receptors to activate downstream signalling molecules, thereby promoting the body's energy metabolism. It acts primarily on the hypothalamus and, via the peripheral nervous system, regulates the energy-metabolising organs (adipose tissue, liver, skeletal muscle, etc.)[6]. Adipose tissue also contains a large number of leptin receptors; this finding demonstrates that leptin may also regulate the physiological activity of adipose tissue via an autocrine pathway[7]. However, in a state of obesity, abnormal proliferation of adipose tissue leads to excessive leptin secretion, resulting in reduced sensitivity to leptin and the development of leptin resistance. This causes disturbances in the body's energy metabolism and insulin resistance, ultimately leading to a series of metabolic syndromes[8–10].

This review aims to analyse how leptin maintains energy homeostasis through different secretion patterns; it discusses the role of various therapeutic approaches for energy homeostasis imbalances in the context of leptin mechanisms; and examines gaps and limitations in the current evidence, as well as areas for future research and clinical translation.

2. Mechanisms Regulating Leptin Secretion and Energy Metabolism Homeostasis

2.1. Primary Mode of Secretion – Endocrine

2.1.1. Target Organ – the Hypothalamus

The effects of leptin on energy metabolism primarily involve central nervous system signalling pathways[3–5,11,12]. A comparison between hypothalamic leptin receptor knockout mice and db/db mice revealed that the two groups exhibit similar metabolic phenotypes. Although the residual leptin signalling in the hypothalamic leptin receptor knockout mice is still capable of regulating their physiological functions to some extent, this compensatory effect is insufficient to reverse their obese phenotype[13,14]. This demonstrates that the hypothalamus is the primary site for leptin-mediated regulation of the body's energy balance. Hypothalamic extensor cells play a key role in this process; for the transcellular transport of leptin, leptin and epidermal growth factor (EGF) must sequentially activate the LepR(leptin receptor):EGFR complex, enabling leptin to traverse the brain and reach its target neurons[15].

The central melanocortin system plays a key role in the satiety effects of leptin and the activation of the sympathetic nervous system[16]. This system comprises a variety of cell types, including neurons expressing pro-opiomelanocortin (POMC), agouti-related protein (AgRP), melanocortin-3 receptor (MC3R) and melanocortin-4 receptor (MC4R).Research has shown that corticotropin-releasing hormone (CRH) promotes the degradation of POMC in the anterior pituitary; it was found that treatment with a CRH antagonist (αCRH) reduces the effect of leptin on the expression of c-fos-like immunoreactivity (cFLI) in the paraventricular nucleus (PVN) and ventromedial hypothalamus (VMH), thereby attenuating leptin's appetite-suppressing and weight-reducing effects.The study also found a strong negative correlation between CRH and peripheral leptin levels, suggesting that leptin stimulates the hypothalamus to release CRH, which in turn inhibits leptin secretion by fat cells, thereby maintaining a dynamic equilibrium[17,18].Hypothalamic POMC and AgRP neurons are primarily located in the arcuate nucleus (ARC). The hypothalamic ARC is a key structure involved in suppressing food intake and stimulating thermogenesis in brown adipose tissue (BAT) and autonomic activity.Studies involving ARC-damaged rats have revealed that leptin's regulation of food intake and body weight requires an intact ARC to be effective, suggesting that the integrity of the ARC plays a crucial role in the functioning of the leptin signalling pathway[19].In the ARC, leptin exerts its appetite-suppressing effect by upregulating the expression of POMC in neurons and downregulating the expression of AgRP in neurons[20]. Among these, signal transduction and transcription activator 3 (STAT3) is a transcription factor involved in a variety of biological

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functions[21]; it acts as a downstream signalling molecule of leptinand serves as an essential 'messenger' for transcriptional regulation in both POMC neurons and AGRP/NPY neurons[22,23]. Other genes in these neurons also play an important role in leptin-mediated energy metabolism. Specific knockout of Sir2-type 1 (Sirt1) in POMC neurons in mice severely impairs the normal binding of leptin to phosphoinositide 3-kinase (PI3K) signalling in POMC neurons, thereby disrupting the remodelling of periglandular white adipose tissue (WAT). At the same time, sympathetic activity and browning of the periglandular fat in mutant mice are also reduced, suggesting that Sirt1 in POMC neurons plays an important physiological role in regulating visceral fat browning[24].Similarly, through genetic knockout and overexpression in POMC neurons, it was found that the presence of the Sequestosome 1 (p62) and zinc-α2-glycoprotein (AZGP1) genes both contribute to increased leptin sensitivity; however, in terms of mechanism, p62 interacts with STAT3, promoting its phosphorylation to initiate POMC transcription and enhance leptin sensitivity. This indicates that p62 can directly regulate STAT3/POMC signalling and enhance leptin sensitivity[25]. AZGP1, on the other hand, enhances leptin-JAK2-STAT3 signalling and increases leptin sensitivity by interacting with acyl-GMP kinase (AGK) to block its ubiquitin-mediated degradation[26].

Cytokin-induced SH2 domain protein (CISH) is co-expressed with the leptin receptor on AgRP neurons in the ARC; the absence of CISH leads to a reduction in the basal expression of AgRP in the arcuate nucleus of the brain. Mice lacking CISH are more sensitive to leptin; although CISH expression itself is not regulated by leptin, CISH's negative regulation of leptin's anorexigenic effects makes it a key regulator of metabolic balance in vivo[27].As our understanding of AgRP neurons has deepened, it has been discovered that they secrete NPY, AgRP and γ-aminobutyric acid (GABA) simultaneously; they are therefore also referred to as NAG neurons. GABAergic RIP-Cre neurons in the arcuate nucleus can coordinately drive energy expenditure, enhance the thermogenic effects of leptin, and prevent diet-induced obesity[28].Neurons in the ARC that express both calcitonin gene-related peptide receptors (Calcr) and leptin receptors include NAG neurons and non-NAG neurons. Experiments have shown that leptin can directly activate LepRb and Calcr in these cells, producing related effects[29].Mice lacking forkhead box O1 (FOXO1) in POMC or AgRP neurons exhibit favourable metabolic characteristics, characterised by a lean body conformation and increased sensitivity to insulin and leptin.Specific knockout of the G protein-coupled receptor 17 (Gpr17) gene in AgRP neurons produces the same phenotype as knockout of the FOXO1 gene in the same cell type, providing preliminary evidence that the G protein-coupled receptor Gpr17 acts as an effector of the appetite-promoting signal from FOXO1 in AgRP neurons[30].

α-Melanocyte-stimulating hormone (α-MSH) is a melanocortin receptor agonist produced by POMC neurons, whereas AgRP is an endogenous melanocortin receptor antagonist[31]. Experiments have shown that α-MSH can enhance leptin sensitivity and preadipocyte proliferation by activating the Neurogenic locus notch homolog 1 (Notch1) signalling pathway, whilst simultaneously inhibiting endoplasmic reticulum stress in preadipocytes[32]. However, there is no direct correlation between α-MSH levels and leptin resistance, demonstrating that there is no direct proportional relationship between α-MSH and leptin concentrations[33].The G protein stimulatory α-subunit (Gsα) facilitates the coupling of various receptors, including MC4R, to intracellular cAMP. Following the generation of Gsα-deficient mice in the dorsomedial hypothalamus (DMH), impaired leptin signalling was observed, accompanied by increased expression of the leptin signalling inhibitor protein tyrosine phosphatase 1B (PTP1B) in the DMH. This may account for the mice's excessive food intake, reduced energy expenditure, decreased locomotor activity and diminished cold-induced thermogenesis[34].The absence of MC3R and MC4R impairs leptin-induced nutrient distribution, appetite suppression and energy metabolism; however, their specific roles require further investigation[35,36].Tropomyosin receptor kinase B (TrkB) signalling originating in the hypothalamus can directly regulate appetite, metabolism and taste preferences downstream of leptin and MC4R[37]. Brain-derived neurotrophic factor (BDNF) is one of the endogenous ligands for the tyrosine kinase receptor TrkB, and theVentromedial Hypothalamus(VMN) is a key site where BDNF inhibits High-Fat Diet(HFD)-induced obesity[38]. VGF (VGF nerve growth factor inducible) is a

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propeptide particularly abundant in the hypothalamus, and its expression is upregulated by environmental enrichment (EE). Research findings indicate that hypothalamic VGF expression is regulated by leptin, melanocortin receptor agonists and food deprivation, and largely parallels BDNF expression[39].

POMC neurons are also found in the nucleus tractus solitarius (NTS) of the medulla oblongata in the brainstem; in recent years, the importance of brainstem nuclei in regulating energy balance has been recognised.The forebrain and hindbrain are connected by extensive synaptic networks, enabling them to act both independently and in concert in regulating the body's energy metabolism. Research has shown that activating leptin receptors in the NTS of the hindbrain can influence the effects of leptin on the forebrain via neural networks[4,40,41]. For example, leptin in the posterior brain enhances the precision of energy balance control by lowering the threshold for leptin signalling in the anterior brain[11]. Under basal conditions, leptin receptors in the posterior brain may antagonise the activity of receptors in the anterior brain in order to protect lean tissue and adipose tissue[42]. Metabolic activity in the forebrain is transmitted via neural pathways to the hindbrain, thereby influencing peripheral tissues. For example, the thermogenic effect of leptin, mediated by RIP-Cre GABAergic neurons in the arcuate nucleus, may involve signals from Paraventricular Hypothalamic nucleus(PVH) neurons being transmitted via NTS GABAergic neurons to neurons in the raphe pallidus (RPa), which in turn activate 5-HT(1A) receptors on local pre-motor sympathetic neurons, ultimately regulating BAT thermogenesis through neuronal hyperpolarisation.Recent research evidence suggests that Lepr neurons in the dorsal dorsomedial hypothalamic nucleus (dDMH) and docosahexaenoic acid (DHA) integrate signals from upstream Lepr neurons in the preoptic area (POA) and the ARC, releasing equal amounts of the neurotransmitters GABA and glutamate, respectively, which are transmitted downstream to regulate thermoregulation and dynamically adapt to various environmental changes, including ambient temperature and energy status.For example, glutamate is released at the synapse and binds to neurons in the globus pallidus anterior, activating pre-sympathetic motor neurons in the RPa, which in turn stimulates thermogenesis in BAT[43–47]. Furthermore, lepr-positive glial cells in the dorsal vagal complex (DVC) at the posterior end of the brainstem may be involved in the transport of leptin into the brainstem, and the leptin-activated neural circuits in the hypothalamus may access white adipose tissue via the DVC[48,49].

In addition to the involvement of the melanocortin system, other hypothalamus-mediated leptin pathways exist within the central nervous system[50,51]. For example, following central leptin administration, obese mice lacking a functional melanocortin system (MC4R-KO mice) exhibit higher interscapular brown adipose tissue (iBAT) temperatures than their wild-type littermates, suggesting that high levels of leptin drive sympathetic activation of iBAT via a non-melanocortin pathway[52]. Research has shown that the VMH is involved in leptin's role in suppressing food intake, suggesting that the VMH also contains LEPR[53,54]. Leptin can directly activate Steroidogenic Factor-1 (SF1)-positive neurons in the VMH, which is a key mechanism underlying leptin's anti-obesity effects.The absence of SF-1 leads to dysregulation of insulin and leptin homeostasis, resulting in increased food intake and delayed-onset obesity under both normal and high-fat dietary conditions. Furthermore, ablation of SF-1 reduces energy expenditure and physical activity, an effect that is more pronounced in aged mice[55,56]. Carnitine palmitoyltransferase 1C (CPT1C) in the VMH acts as a downstream regulator of AMP-Activated Protein Kinase (AMPK), which governs BAT thermogenesis. Knocking out CPT1C in mice inhibits BAT thermogenesis and weight loss, demonstrating that CPT1C is essential for leptin-driven BAT thermogenesis[57].

Neurons in the PVH also express leptin receptors, which mediate the anti-obesity and thermogenic effects of leptin. Experiments have shown that microinjection of rAAV-lep into the PVH of diet-induced obese rats reduces energy intake and increases energy expenditure; it normalises body weight and blood levels of leptin, insulin, free fatty acids and glucose, whilst gastric ghrelin secretion increases over the extended observation period. This indicates that enhancing the response to leptin in the PVH can reverse diet-induced obesity and hyperinsulinaemia, and block the central stimulatory effects of elevated endogenous ghrelin on food intake and obesity[58].Secondly, leptin

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can target a specific subpopulation of Oxytocin (OXT) neurons within the PVH to reduce body weight[59].The Single-Hearted Origin 1 gene (Sim1) is highly expressed in the PVH and parts of the amygdala. Studies have shown that the specific loss of LepR in Sim1 neurons leads to a reduction in both peripheral and core body temperature in mice, decreased energy expenditure at room temperature, and impaired non-shivering thermogenesis in response to cold stimulation. This demonstrates the role of LepR signalling in Sim1 neurons in regulating body weight, core body temperature and non-shivering thermogenesis[60].

In the nervous system, in addition to neurons, there are also large numbers of glial cells, which perform auxiliary functions such as supporting, nourishing, protecting and insulating neurons; indeed, the central nervous system effects of leptin are also dependent on the support of glial cells. Experiments have shown that knocking out the leptin receptor in astrocytes can prevent morbid obesity induced by a high-fat diet and leptin receptor mutations in neurons, suggesting that the absence of leptin signalling in astrocytes helps to better preserve leptin signalling in neurons. This demonstrates that there is a competitive and negative regulatory relationship between leptin signalling in neurons and that in astrocytes. Astrocyte leptin signalling is a key factor contributing to obesity, hyperleptinaemia and impaired neuronal leptin signalling[61].(Figure 1)

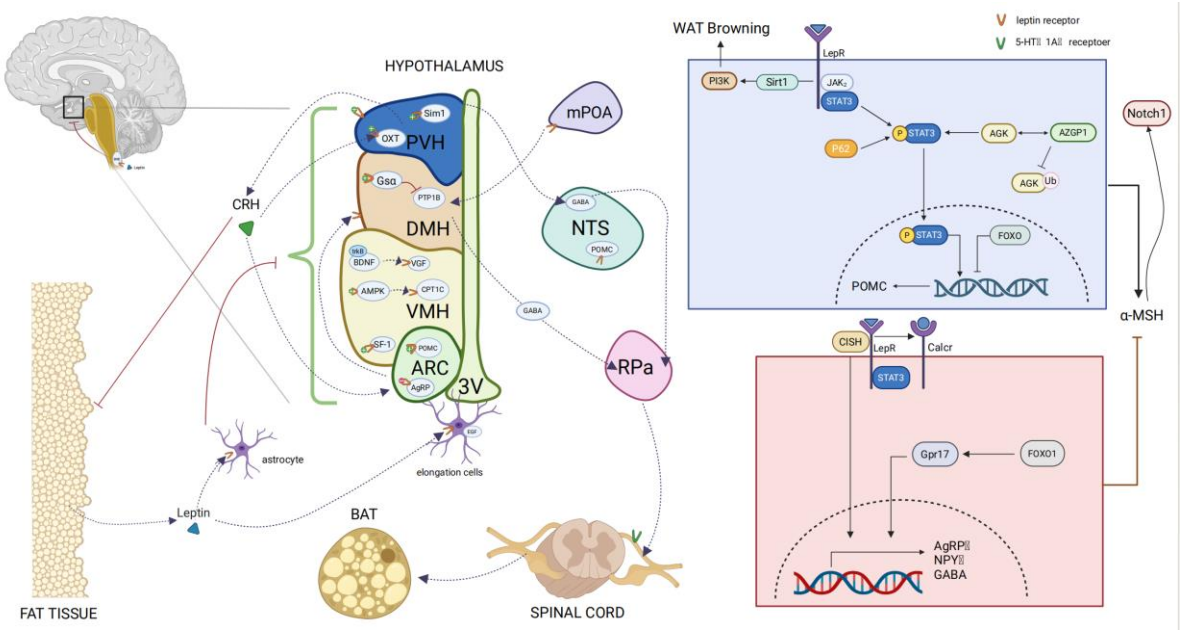

Figure 1. Neuro-humoral regulation.CRH: Corticotropin-Releasing Hormone; Sim1:Single-minded homolog 1; OXT: Oxytocin; Gs*α*:G-protein subunit alpha (stimulatory); PTP1B: Protein Tyrosine Phosphatase 1B; trkB: Tropomyosin receptor kinase B; BDNF: Brain-Derived Neurotrophic Factor; AMPK: AMP-Activated Protein Kinase; SF-1: Steroidogenic Factor 1; VGF: VGF nerve growth factor ind ucible; CPT1C: Carnitine Palmitoyltransferase 1C; POMC: Pro-opiomelanocortin; AgRP: Agouti-related peptide; GABA: Gamma-Aminobutyric Acid; CISH: Cytokine-Ind ucible SH2-containing protein; Calcr: Calcitonin receptor; Gpr17: G protein-coupled receptor 17; FOXO1: Forkhead box protein O1; PI3K: Phosphoinositide 3-kinase; Sirt1: Sirtuin 1; JAK2: Janus kinase 2; STAT3: Signal Transducer and Activator of Transcription 3; P62: Sequestosome 1; AGK(ub): ubiquitinated Acylglycerol Kinase; AZGP1: Zinc-alpha-2-glycoprotein; Notch1: Neurogenic locus notch homolog protein 1; FOXO: Forkhead box O transcription factors;*α*-MSH: Alpha-melanocyte-stimulating hormone; PVH: Paraventricular Hypothalamic nucleus; DVC: Dorsal Vagal Complex; DMH: Dorsomedial Hypothalamus; VMH: Ventromedial Hypothalamus; ARC: Arcuate Nucleus; 3V: Third Ventricle; mPOA: medial Preoptic Area; NTS: Nucleus Tractus Solitarius; RPa: Raphe Pallid us nucleus.

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2.1.2. Target Organ – the Liver

Current research indicates that leptin's primary effect on the liver is to improve glucose metabolism, such as by enhancing glycogen storage and reducing gluconeogenesis; these may constitute important compensatory mechanisms for the suppression of insulin secretion. Leptin can also temporarily enhance insulin's effect on glycogen synthesis, a phenomenon associated with the inhibition of phosphorylase A; this effect can be reversed by brief incubation with glucagon[62,63].In well-differentiated hepatocellular carcinoma cells, treatment with leptin alone had no effect on the insulin signalling pathway; however, pretreatment with leptin transiently enhanced insulin-induced tyrosine phosphorylation of Insulin Receptor Substrate 1 (IRS-1) and the binding of PI3K to IRS-1, whilst simultaneously inhibiting the tyrosine phosphorylation of Insulin Receptor Substrate 2 (IRS-2) and the binding of PI3K to IRS-2. Leptin can also induce serine phosphorylation of Protein Kinase B (PKB) and glycogen synthase kinase 3, but its potency is lower than that of insulin, and the effects of these hormones are not simply additive. These results indicate that there are complex interactions between leptin and insulin signalling pathways[64].

2.1.3. Target Organ – the Muscle

As the primary organ of energy metabolism, skeletal muscle is also directly influenced by leptin[65]. Leptin resistance induced by obesity is clearly manifested in skeletal muscle; the onset of obesity inhibits leptin-stimulated fatty acid oxidation in skeletal muscle[66]. Leptin-stimulated fatty acid oxidation in skeletal muscle can be mediated through pathways involving AMPK and acetyl-CoA carboxylase (ACC); however, this effect is confined to muscle fibres, and the function of this pathway is impaired in the obese state. This suggests that leptin resistance in obesity may be associated with impaired fatty acid oxidation via this pathway[67].In cellular experiments, treatment of C2C12 myotubes with leptin rapidly induced the expression of acyl-CoA oxidase (ACOX), demonstrating that, in the early stages of overnutrition and prior to the development of leptin resistance, peroxisomes may work in conjunction with mitochondria to clear excess lipids from non-adipose tissues[68]. However, an increase in leptin concentration alone does not affect skeletal muscle responsiveness to leptin; for instance, raising circulating leptin levels to concentrations comparable to those in obese individuals enhances the AMPK signalling pathway in human skeletal muscle, leading to increased fatty acid oxidation[69]. Furthermore, experiments have identified the N-terminal peptide (17-peptide) of leptin as the primary site responsible for its effects on glucose metabolism and energy homeostasis[70]. The mechanisms underlying whether obese patients exhibit impaired leptin-stimulated fatty acid oxidation in skeletal muscle, alongside increased fatty acid uptake and esterification, require further investigation.

2.2. Supplementary Mechanism—Autocrine Regulation

Leptin primarily regulates various signalling molecules and pathways by binding to leptin receptors; it is involved in carbohydrate, lipid and energy metabolism, reduces food intake and increases thermogenesis, thereby promoting weight loss[57,71]. Adipose tissue serves not only as a secretory organ for leptin but also as its primary target organ. Results from studies involving the knockout of leptin receptors in mouse adipose tissue, as well as in vitro studies of leptin's effects on rat adipocytes, indicate that adipocytes can regulate energy metabolism in adipose tissue via an autocrine pathway without the involvement of the central nervous system[72,73].

Early in vitro studies have shown that leptin can directly promote fatty acid oxidation in fat cells, thereby increasing lipid consumption; it can also directly inhibit insulin-mediated fat synthesis in fat cells[74–76]. Adenovirus-induced leptin overexpression rapidly reduces body fat in rats, promotes the oxidation and breakdown of fatty acids in white adipocytes, leading to the atrophy of these cells, which become filled with mitochondria that are smaller than those found in brown adipocytes.This phenomenon primarily stimulates mitochondrial biogenesis by activating STAT3 and Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-α (PGC-1α) in fat cells. Studies on ASKO mice,

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which specifically lack the STAT3 gene in adipocytes, have shown that leptin-induced lipolysis in these mice is impaired, suggesting that leptin directly regulates lipid metabolism via the STAT3 molecule in adipocytes[77]. It was found that direct treatment of adipocytes with leptin significantly upregulated the mRNA expression of PGC-1α, cytochrome c (Cytc) , carnitine palmitoyltransferase 1 (CPT1), Uncoupling Protein 2(UCP2) and Uncoupling Protein 3 (UCP3), genes that play a crucial role in fatty acid oxidation and energy expenditure; simultaneously, fatty acid synthase (FAS) expression in adipocytes was reduced, whilst acetyl-CoA carboxylase (ACC) expression and the phosphorylation levels of AMPK were both significantly elevated.These results indicate that leptin stimulates mitochondrial biogenesis, increases fatty acid oxidation, thermogenesis and energy expenditure by activating PGC-1α[72,78,79]. However, the effect of leptin on PGC-1α is significantly attenuated in PPARα-knockout mice, demonstrating that PPARα in adipocytes plays a crucial role in the action of leptin[80]. Administration of exogenous leptin to ob/ob mice revealed that, following leptin treatment, the levels of hormone-sensitive lipase (HSL), UCP2, adrenergic receptor 3 (ADR3), mitofusion protein 2 (Mfn2), sirtuin 3 (Sirt3), sterol regulatory element-binding factor 1 (SREBF1), B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X protein (Bax), Cysteine-aspartate protease 3 (Caspase 3), tumour necrosis factor α (TNF-α), adiponectin and angiopoietin 2 (Ang-2); whilst the expression of stearoyl-CoA desaturase 1 (SCD1), FAS and retinol-binding protein 4 (RBP4) was reduced.These results indicate that leptin treatment in ob/ob mice alters gene expression in adipose tissue, which not only promotes lipid mobilisation and energy expenditure but also contributes to apoptosis and angiogenesis[81]. Following exogenous leptin administration in rats, adipose tissue also exhibited similar apoptotic features, including inter-nucleosomal DNA breaks, elevated levels of DNA strand breaks, reduced total DNA content and decreased cell volume. However, these apoptotic features were not observed in rats maintained on a matched diet or in other tissues of the leptin-treated rats[82].

The cytokine signalling suppressor of growth hormone 3 (SOCS3) is considered a leptin-resistant factor; in obese rats fed a high-fat diet, the mRNA and protein levels of SOCS3 in epididymal fat were significantly increased. In vitro experiments revealed that after incubating SOCS3-knockdown adipocytes with 50 nM leptin for 6 hours, the mRNA expression of acetyl-CoA carboxylase (a marker of de novo fatty acid synthesis) was reduced, whilst the expression of acetyl-CoA oxidase mRNA (a marker of fat oxidation) increased, demonstrating that SOCS3 acts as a negative regulator of leptin-mediated fatty acid oxidation in adipocytes[83]. SOCS2 is another member of the SOCS family and is widely expressed in muscle, nerve, pancreatic and adipose tissues. Studies have shown that leptin increases SOCS2 mRNA levels in mouse inguinal adipose tissue; however, it has been found that genes associated with fatty acid oxidation that are up-regulated by leptin ,such as PGC-1α, (Nuclear Respiratory Factor 1) NRF-1, TFAM, CPT-1b, AOX1, Cytochrome c Oidase subunit 2 (COX2) and UCP2 are attenuated by SOCS2. Furthermore, SOCS2 reduces the levels of mitochondrial complexes I and III, the fatty acid oxidase MCAD, long-chain acyl-CoA dehydrogenase (LCAD), and cytochrome C, as well as the release of free fatty acids. This indicates that SOCS2 exerts a negative effect on mitochondrial fatty acid oxidation, and these effects are closely linked to the LepR/JAK2/AMPK pathway[84].

Neuromodulatory protein B (NMB) is a member of the iridin-like peptide family and has been shown to reduce food intake when administered systemically. Its expression in adipose tissue is regulated by leptin; following leptin administration to both obese and control mice, mRNA expression of NMB in adipose tissue is reduced in both groups. Given its anorexigenic effects, it may represent a novel physiological mechanism for regulating appetite via the ‘adipose-hypothalamic axis’[85]. Activation of fatty acid-binding protein 4 (FABP4) reduces the expression of leptin, CPT-1 and AOX1 in mouse adipocytes; conversely, leptin treatment downregulates FABP4. FABP4 can reverse leptin-induced mitochondrial fatty acid oxidation, and this effect is closely associated with the inhibition of the Akt/mTOR signalling pathway[86](Figure 2).

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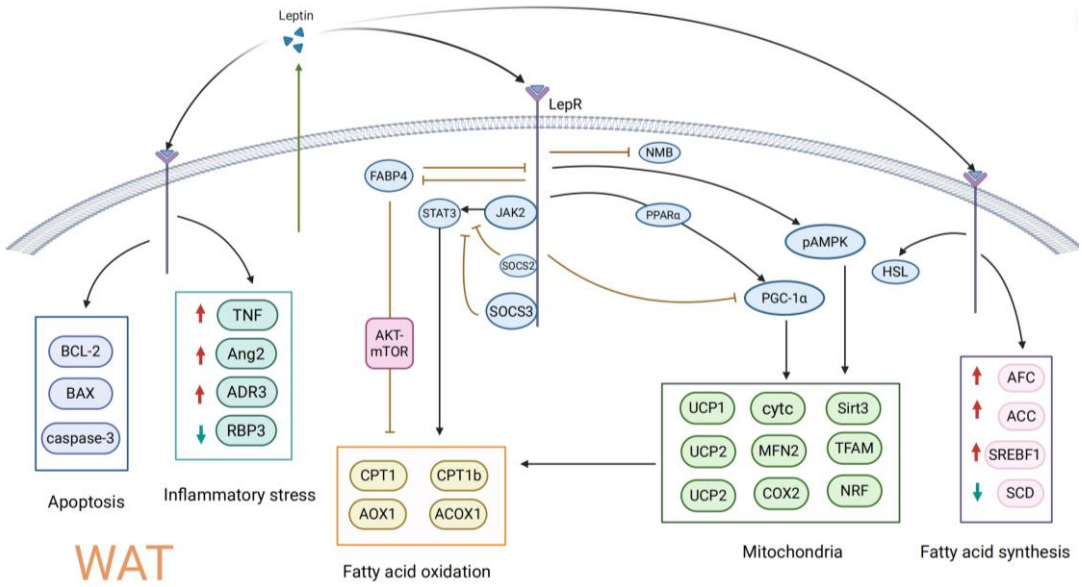

Figure 2. Autocrine regulation. BCL-2: B-cell lymphoma 2; BAX: BCL2-associated X protein; Caspase3: Cysteinyl aspartate specific proteinase 3; TNF: Tumor Necrosis Factor; Ang2: Angiopoietin 2; ADRB3: Ad renoceptor Beta 3; RBP3: Retinol-Binding Protein 3; CPT1: Carnitine Palmitoyltransferase 1; CPT1b: Carnitine Palmitoyltransferase 1B; AOX1: Aldehyde Oxidase 1; ACOX1: Acyl-CoA Oxidase 1; FAS: Fatty Acid Synthase; ACC: Acetyl-CoA Carboxylase; SREBP-1: Sterol Regulatory Element-Binding Transcription Factor 1; SCD: Stearoyl-CoA Desaturase; UCP1: Uncoupling Protein 1; UCP2: Uncoupling Protein 2; UCP3: Uncoupling Protein 3; Cyt C: Cytochrome C; MFN2: Mitofusin 2; COX2: Cytochrome c Oxidase Subunit II; Sirt3: Sirtuin 3; TFAM: Transcription Factor A Mitochondrial; NRF: Nuclear Respiratory Factor; FABP4: Fatty Acid-Binding Protein 4; AKT-mTOR: AKT (Protein Kinase B) - mechanistic Target of Rapamycin; STAT3: Signal Transducer and Activator of Transcription 3; JAK2: Janus Kinase 2; SOCS2: Suppressor of Cytokine Signaling 2; SOCS3: Suppressor of Cytokine Signaling 3; LepR: Leptin Receptor; NMB: Neuromedin B; PPARα: Peroxisome Proliferator-Activated Receptor Alpha; PGC-1α: Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha; pAMPK: phosphorylated AMP-Activated Protein Kinase; HSL: Hormone-Sensitive Lipase; WAT: White adipose tissue.

3. The Circadian Rhythm of Leptin Secretion

The metabolic effects of leptin in adipose tissue exhibit circadian rhythms[87,88]. It has been demonstrated that the circadian rhythm of circulating leptin levels is determined by the timing of food intake. Mice typically feed in the dark; however, whilst a short-term high-fat diet eliminates circadian fluctuations in plasma leptin levels[89], feeding mice during the day may also cause circadian-related fluctuations in their central leptin sensitivity, thereby inducing leptin resistance[90]. Leptin resistance is a hallmark of human obesity and plays a key role in obesity and metabolic syndrome induced by circadian dysfunction[91].

4. Therapeutic Transformation

4.1. Medicines

Some obese patients exhibit leptin resistance; consequently, leptin sensitizers, rather than leptin itself, are expected to serve as therapeutic agents for obesity. Leptin sensitizers are primarily intended to address conditions characterised by excessively high leptin concentrations or leptin resistance. Studies have shown that oral administration of 1,3-butanediol (BD) has a therapeutic effect on obese mice with leptin resistance; this effect is closely associated with increased ATP concentrations in the hypothalamus and elevated plasma levels of β-hydroxybutyrate[92]. Inhibitors of the cellular histone

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deacetylase 6 (HDAC6), such as tolvaptatin A, are also potent leptin sensitizers and anti-obesity agents. Mechanistically, they confer central leptin sensitivity by inhibiting peripheral HDAC6. Furthermore, the anti-obesity effects of tolvaptatin A are attenuated in animals accompanied by a reduction in the central leptin-melanocortin feedback loop, including in db/db and MC4R-KO mice[93]. JD5037, a peripherally restricted CB_1R inverse agonist, reverses hyperleukaemia by reducing the expression and secretion of leptin in adipocytes and increasing renal clearance of leptin, thereby enhancing the sensitivity of obese mice to endogenous leptin[94]. Resveratrol also reduces leptin secretion from fat cells in rats[95]. Treatment with 5-aminoimidazole-4-carboxamide-1-β-D-furanoside (AICAR) can also increase hypothalamic leptin sensitivity, thereby reducing fat content[96]. Rapamycin, an inhibitor of the mammalian target of rapamycin (mTOR), reduces food intake and fat mass in diet-induced obese mice, but is ineffective in animals with leptin deficiency. Bowen Tan recently discovered that increased mTOR activity in POMC neurons leads to leptin resistance, whilst rapamycin restores the action of leptin on POMC neurons. This suggests that rapamycin can suppress the enhanced activity of mTOR, thereby improving leptin resistance and alleviating associated symptoms of obesity[97].

Obesity patients often experience a ‘weight loss plateau’ whilst trying to lose weight, and the advent of leptin sensitisers may well break the vicious cycle of ‘weight loss followed by weight regain’. This is because when a person loses weight, the number of fat cells decreases and the secretion of leptin falls accordingly; upon receiving this signal, the brain activates a compensatory mechanism by increasing appetite and reducing metabolic rate.Leptin sensitizers not only restore the brain’s sensitivity to high concentrations of leptin during periods of obesity characterised by leptin resistance—thereby directly suppressing appetite, boosting metabolism and promoting weight loss—but also, once weight has been lost and leptin levels have returned to the normal range, they can help maintain weight and prevent weight regain by ensuring the brain remains sensitive to these normal leptin levels.However, most leptin sensitizers currently available are effective only in cases of high leptin concentrations and leptin resistance, and do not produce any significant response in individuals with normal leptin levels. Consequently, future research could explore approaches that go beyond the sole use of leptin sensitizers, such as integrating them into a comprehensive treatment regimen—for example, by combining them with other types of medication—or utilising them as a chronic disease management medication for long-term use to regulate energy balance and maintain normal physiological states.However, even though many similar drug candidates have shown promising results in laboratory studies, there is still a long way to go from animal trials to the successful development of drugs that are both effective and safe for human use. At present, there is no ‘leptin sensitiser’ in the strict sense of the term that has been widely approved for clinical use. Some existing drugs (such as the GLP-1 receptor agonists semaglutide and tirzopentide) have been found to potentially improve leptin sensitivity indirectly, in addition to their primary functions, but they are not dedicated leptin sensitizers.

In addition to leptin sensitizers, there are also drugs that exert leptin-related anti-obesity effects by activating downstream leptin pathways. Konjac glucomannan (KGM) significantly reduced leptin and fatty acid signalling in adipose tissue, activated thermogenesis in brown adipose tissue, suppressed the expression of POMC and activated the expression of AgRP, thereby reducing food intake and increasing energy expenditure[98].The black soy isoflavone-isoflavone-free peptide mixture (BSP) activates the leptin-downstream JAK2/STAT3 signalling pathway in cellular models and increases STAT3 phosphorylation levels in the hypothalamus of ob/ob mice. BSP also increases the phosphorylation of AMPK and acetyl-CoA carboxylase in C2C12 myoblasts in a dose-dependent manner. These results suggest that BSP reduces appetite and high-fat diet-induced weight gain through leptin-like STAT3 phosphorylation and AMPK activation, particularly when combined with exercise[99]. In vitro studies have shown that vanadates can also enhance leptin-induced phosphorylation of JAK2 and STAT3 in CHO cells. Furthermore, vanadates (PTP inhibitors) reverse the inhibitory effect of SOCS3 on leptin-induced STAT3 phosphorylation, thereby exerting a therapeutic effect against obesity[100].Tungstate also relies on the leptin system to exert its weight-

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reducing effects, specifically by increasing energy expenditure in animals, including the expression of key genes involved in BAT thermogenesis. Furthermore, it can influence the gene expression of the hypothalamic neuropeptides NPY, AgRP and GART, which are regulated by leptin[101]. A water extract of Gastrodia elata (GEB) containing phenolic compounds reduces fat accumulation in adipocytes by activating lipid oxidation and enhancing leptin signalling, thereby reducing insulin resistance in diet-induced obese rats[102].The improvement in energy homeostasis induced by the Intestinal Blood Stasis-Resolving Decoction (CCEET) and the Modified Intestinal Blood Stasis-Resolving Decoction (MCCEET) is associated with the enhancement of the hypothalamic leptin signalling pathway, including increased signal transduction and phosphorylation of transcription factors, as well as reduced phosphorylation of AMPK[103]. Studies have also shown that PNS (Panax notoginseng saponins) can participate in the remodelling of brown adipose tissue by regulating the leptin/AMPK/STAT3 signalling pathway induced by the gut microbiota. This leads to increased energy expenditure and a reduction in obesity[104].

4.2. Diet

Fasting significantly reduces the concentration of leptin in the blood. This is a normal physiological response by which the body adapts to a state of energy deprivation; its primary purpose is to conserve energy and stimulate appetite, but this effect diminishes over time. On average, leptin levels drop significantly by 66% in the first week, after which the rate of decline gradually slows. However, changes in circulating leptin levels associated with food restriction do not reflect changes in body fat mass.In obese patients, fluctuations in energy intake over a period of days or weeks are the primary determinants of plasma leptin concentrations; leptin levels correlate with changes in blood glucose and can override the regulatory effects of body fat mass. In large animals such as horses, short-term fasting reduces leptin levels without significantly altering body weight[105,106]. However, the decline in leptin levels resulting from acute fasting in obese patients was significantly lower than that in a control group with a matched body mass index who maintained a normal diet, and this pattern persisted for up to 12 weeks. Following the end of the fasting period, although serum leptin levels rose again, they remained significantly lower than those in the control group[107]. Compared with lean individuals, fasting overweight men exhibited altered postprandial acute energy substrate utilisation, with reduced carbohydrate oxidation and strongly inhibited lipid oxidation, which may be attributed to some degree of leptin resistance. These data also suggest that if these changes in acute energy substrate utilisation persist over a long period, they may explain long-term physical obesity[108]. Furthermore, the study found that leptin inhibits excitatory synaptic input to neurons in the lateral hypothalamic area (LHA) that project to the ventral tegmental area (VTA) and express orexin and melanin. Both energy expenditure induced by acute food deprivation and energy over-storage caused by a high-fat diet attenuate the inhibitory effect of leptin on synaptic transmission[109].

Research has also found that dietary patterns can influence circulating leptin concentrations and the action of leptin; for example, a ketogenic diet characterised by very low carbohydrate and high fat intake exacerbates insulin resistance in non-obese rats with type 2 diabetes and impairs energy and glucose homeostasis by attenuating hypothalamic leptin signalling[107**Error! Reference source not found.**]. Conversely, increasing sucrose intake in the diet leads to leptin resistance; experiments have revealed that the mechanism underlying this is associated with differences in specific sites of leptin signalling in the hypothalamus[110,111]. However, when a low-fat diet is adopted in place of a high-sugar, high-fat diet, leptin responsiveness rapidly returns to normal[112]. Cross-sectional studies have found that the Mediterranean diet—characterised by a low intake of saturated fatty acids (7–8%) and a higher intake of unsaturated fatty acids—is likely to influence body mass index and maximum oxygen uptake via the mediating action of leptin[113,114].Some studies also suggest that carbohydrate intake increases energy expenditure and leptin levels more effectively than fat intake, and that elevated circulating leptin levels contribute to the weight-loss benefits of a high-carbohydrate, low-fat diet[110,115,116]. Therefore, when following a high-fat, low-carbohydrate diet,

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the resulting decrease in circulating leptin is likely to contribute to weight gain.The post-transcriptional regulation of leptin, as well as the development and reversal of leptin resistance, also involve the availability of substrates; even without regulating the rate of lipolysis in fat cells, leptin is capable of directly modulating the balance of nutrient utilisation. This regulatory mechanism is sufficient to regulate fat mass without altering food intake or energy expenditure[117].However, other experimental data suggest that, rather than the structure, proportions and combinations of nutrients in the diet, leptin is actually more closely correlated with the absolute intake of the three macronutrients than with their percentages[118]. For example, leptin concentrations are positively correlated with the carbohydrate content of the diet[119], and carbohydrate intake can offset the exercise-induced reduction in circulating leptin[120]. Nevertheless, several experimental findings indicate that leptin levels' response to energy restriction, as well as the relationship between leptin and insulin, are highly correlated with the composition of dietary fatty acids.The fatty acid composition of the diet is a key determinant of circulating leptin levels in induced obesity. In summary, the composition of dietary fatty acids determines circulating leptin levels. Studies have shown that, compared with the butter group, rats fed ad libitum on fish oil and safflower oil had plasma leptin concentrations 60% higher, indicating a hyperleptinaemic effect in animals consuming a diet rich in polyunsaturated fatty acids, which can be normalised to the levels observed with saturated fat consumption through mild energy restriction. This suggests that modifying the diet can improve the role of leptin in obesity[121].This may be related to the number of carbon atoms in fatty acids. Studies investigating the effects of short-chain fatty acids (SCFAs) and long-chain fatty acids (LCFAs) on leptin expression in bovine adipocytes found that removing foetal bovine serum and reducing glucose levels in the culture medium of differentiated adipocytes decreased leptin mRNA expression. Subsequent addition of acetate, butyrate or propionate restored and increased leptin expression in a dose-dependent manner, whereas the addition of LCFAs inhibited leptin expression. Mechanistically, leptin expression in bovine adipocytes is upregulated by SCFAs via stimulation of G protein-coupled receptors, whereas it is downregulated by LCFAs[122].

4.3. Exercise

Traditionally, it has been believed that weight loss through exercise is achieved primarily by burning calories. However, research suggests that exercise itself acts as a powerful biological signal that directly regulates the levels and sensitivity of the key hormone leptin, thereby improving obesity at both the hormonal and neural levels. It is not merely a matter of 'burning calories', but rather of 'resetting' the body's energy regulation system.

For example, exercise can lower leptin levels. Following exercise, leptin concentrations in the blood decrease (both at the mRNA level and in plasma), but this effect is delayed; this suggests that exercise does not reduce the leptin gene itself, but rather regulates its 'expression' process[123–125]. Research has found that a decrease in blood leptin levels can be observed within a few hours of acute exercise (a single session), whilst there is no corresponding change in fat mass. This suggests that exercise directly triggers a physiological mechanism that instructs fat cells to 'reduce the synthesis and secretion of leptin', rather than relying on a reduction in fat cell size to decrease secretion[126].This rapid decline in leptin concentration, independent of body fat mass, is likely an adaptive response by the body; it temporarily reduces 'satiety signals', helping to ensure that individuals retain sufficient appetite after exercise to consume the energy and nutrients needed to repair the body. This suggests that every bout of exercise offers immediate metabolic benefits[124]. The mechanism is likely that a single bout of exercise immediately enhances the hypothalamus's response to leptin signals (such as increased ERK1/2 phosphorylation), thereby boosting energy expenditure[127]. Following long-term exercise training, however, overall leptin levels decline; this is partly due to a reduction in total body fat, which indirectly affects leptin production.More importantly, the brain has become more sensitive to leptin; even though total leptin levels have fallen, the brain's response to it has become stronger (this is why exercise has a more pronounced effect on people with normal metabolism, as their leptin system is inherently more

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sensitive)[128,129].Furthermore, the experiments revealed that when the GP130 protein was knocked out in mice, the weight-loss effects of exercise were significantly reduced, suggesting that exercise relies on IL-6 signals released by fat cells to enhance the hypothalamus's sensitivity to leptin and insulin. This demonstrates that the effects of exercise are not mediated by a single hormone, but rather result from the synergistic interaction of multiple hormones and cytokines—including leptin, insulin and IL-6—at the network level[130].

Furthermore, obesity is often accompanied by chronic inflammation, which interferes with leptin signalling; exercise can suppress inflammation and thus help restore the function of the leptin signalling pathway. However, research has shown that it is moderate-intensity exercise that effectively improves leptin resistance and inflammation, whereas high-intensity exercise may trigger a strong inflammatory response, which could actually offset the benefits of exercise in improving leptin resistance[131]. Furthermore, studies have found that following exercise and dietary interventions, adipose tissue in different areas of the body responds differently (glutes vs. abdomen). This explains why changes occur at different rates in various parts of the body during fat loss[132].

It is well known that exercise and controlling food intake are key strategies for managing obesity. For over a decade, scientists have been investigating whether leptin plays a role in the effects of exercise on obesity. Research on exercise interventions indicates that dietary control can reduce body weight and leptin levels, but only when combined with exercise can it effectively improve leptin resistance and achieve long-term weight management[133]. Otherwise, at low leptin levels, the body is more prone to feeling hungry and entering an energy-saving mode (a plateau or weight regain). Furthermore, for obese individuals, starting with moderate-intensity aerobic exercise may be an effective and lower-risk method for improving leptin sensitivity and suppressing inflammation[134].

5. Summary and Outlook

Obesity has long been a major challenge in the field of healthcare, and finding solutions to this problem has become a key area of research within the scientific community. Energy metabolism encompasses both energy intake and energy expenditure, and ensuring that energy expenditure exceeds energy intake has long been regarded as the primary method for addressing obesity. As the first adipokine to be discovered, leptin has been extensively studied for its role in reducing food intake and increasing energy expenditure. Although some progress has been made in understanding the effects of leptin on metabolic function and its underlying molecular mechanisms, there remains a considerable distance before it can be applied as a therapeutic agent in clinical practice. Elucidating the network pathways through which leptin exerts its effects will facilitate the exploration of its immense potential in the treatment of metabolic diseases. In summary, understanding the role of leptin in energy metabolism helps to uncover new approaches for increasing energy expenditure and reducing energy intake, which is of great significance for the research, prevention and treatment of fat accumulation associated with metabolic disorders.

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