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Leptin Receptor Gene and Its Role in Obesity: A Comprehensive Narrative Review of Current Evidence

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Abstract

Background:
Obesity is a disorder of multiple factors and is influenced by the genetic, environmental, and behavioral factors. The leptin receptor gene (LEPR) is the one that basically regulates the energy balance by being the mediator of leptin signaling that is the controller of appetite and metabolism. The genetic variations of LEPR are the major causes of resistance to leptin, which is the main mechanism that leads to obesity.
Objective:
This review exhaustively delves into the aspects of the LEPR gene such as its structure, function, polymorphisms, and signaling pathways and also the role of the gene in the obesity pathogenesis, accompanying metabolic disorders, and the prospects of therapy.
Methods:
The research findings from molecular, genetic, and clinical studies were discussed through a narrative synthesis of evidence. The research mainly focused on the mechanistic aspects of the LEPR gene in obesity, associations at population levels, and pharmacogenomic implications.
Results:
LEPR polymorphisms especially Q223R, K109R, and K656N alter the receptor affinity as well as the subsequent JAK2–STAT3, MAPK, and PI3K signaling thus the susceptibility to obesity and the metabolic effects. Epigenetic changes and chronic inflammation contribute to the aggravation of leptin resistance. Besides, LEPR defect has also been proven to be the cause of type 2 diabetes, metabolic syndrome, PCOS, and cardiovascular diseases. The newly proposed interventions comprise gene therapy, correction through CRISPR, and RNA therapeutics aimed at leptin sensitization.
Conclusion:
The LEPR gene is one of the most important molecular factors that lead to obesity and disorders related to it. The combination of genetic, epigenetic, and pharmacogenomic knowledge with personalized obesity medicine has the power to bring about a complete change in the ways of prevention and treatment through the restoration of leptin sensitivity and metabolic balance

Introduction

Obesity is a global epidemic that has grown to an alarming size and poses major threats to human health and socioeconomic stability. Its prevalence has risen dramatically in both developed and developing countries over the last several decades [1]. WHO reports that currently there are over a billion people globally who are either

overweight or obese among them more than 340 million children and adolescents. Obesity is a complex and chronic disease that is defined as excessive fat accumulation caused by an energy imbalance of the body. It is a leading cause of metabolic and cardiovascular diseases such as type 2 diabetes, dyslipidemia, hypertension, coronary artery disease, nonalcoholic fatty liver disease, and some cancers [2]. In addition to this heavy physiological burden, obesity also brings psychological, social, and economic problems of considerable magnitude.

While environmental and behavioral factors leading to obesity such as a sedentary lifestyle, unhealthy eating patterns, and decreased physical activity are well known, the role of genetics in the predisposition to obesity is increasingly being recognized by a substantial body of scientific literature. Studies on twins and families indicate that genetic factors may account for 40–70% of the differences in BMI that exist between individuals. This understanding has triggered extensive research aimed at the identification of genes involved in the regulation of appetite, metabolism, and body fat. The leptin and leptin receptor (LEP–LEPR) system is arguably the most significant molecular pathway controlling energy balance among these [3].

The identification of leptin by Friedman et al. in 1994 changed the concept of obesity to a neuroendocrine disorder and cleared the way for studies on obesity as a condition caused by complex interactions of the body rather than a simple result of lack of restraint in eating. Leptin is a hormone of 16-kDa, which comes from fat cells and is encoded by the LEP gene located at chromosome 7q31.3 [4]. It acts as the major signal in the feedback circuitry between fat and the brain, whereby the hypothalamus, as the main target, receives the signal and suppresses appetite while promoting energy expenditure. The function of leptin in normal physiology is to prevent body weight from going above a certain level by inducing the signal of energy surplus. So, in the case of increased fat, leptin concentration also goes up, making eating less attractive and encouraging the release of stored energy; on the other hand, if one is starved, and therefore leptin is low, hunger is induced, and energy saving mechanisms are activated [5].

Leptin does biological activity through a receptor with which it binds, i.e., the leptin receptor (Ob-R) is the protein that is coded for by the LEPR gene and is located on chromosome 1p31. The protein receptor for leptin is a member of the class I cytokine receptor family and has many isoforms as a result of alternative splicing. These include the long isoform (Ob-Rb), which is considered to have a full intracellular signaling domain that is of great importance in the subsequent activation of the JAK signal transducer and STAT (STAT) pathway [6]. The short isoforms (Ob-Ra, Ob-Rc, Ob-Rd, Ob-Re) work in leptin transport, removing, and signaling of the peripheral tissues. Problems in regulation or mutation of the protein receptor for leptin interfere with this signaling sequence, which results in a state of leptin resistance that is at the core of both monogenic and polygenic forms of obesity [7].

The LEPR gene is a major player in keeping the energy balance and regulating body weight. It does so by affecting glucose metabolism, lipid homeostasis, and neuroendocrine functions. Many polymorphisms in the LEPR gene have been discovered and heavily researched in connection with obesity and its metabolic side effects[8]. In fact, Q223R (rs1137101), K109R (rs1137100), and K656N (rs8179183) are the three most commonly studied polymorphic loci of the LEPR gene. These polymorphisms might change how receptor binding affinity works, how leptin is transported through the blood–brain barrier, and how efficiently intracellular signaling is carried out. To cite an example, an association of Q223R genetic variation with increased serum leptin concentration, higher BMI, insulin resistance, and dyslipidemia was confirmed in several ethnic groups. Nonetheless, the degree and sign of the relationship vary among different populations, thus implying a gene-environment interaction that is complex[9].

The reasons for mapping out the LEPR gene are not limited to finding the hereditary background of obesity. It is instrumental in shedding light on the resistance mechanisms of leptin – a condition in which increased circulating leptin fails to mediate its anorexigenic effects. Leptin insensitivity results in sustained hyperphagia, lowered energy expenditure, and gradual increase in body weight[10]. At the same time, it is possible that impaired leptin transport, receptor mutations, ineffective JAK-STAT or phosphatidylinositol 3-kinase (PI3K) signaling, and chronic inflammation in the hypothalamus are the causes of this process. Hence, discovering LEPR genetic variations as well as molecular malfunctionings is a prerequisite for formulating individualized obesity therapies and specific drug interventions aiming at recuperation of leptin responsiveness[11].

Besides, knowledge about LEPR gene has far-reaching effects on the metabolism and neuroendocrine systems. While being the main regulator of the appetite, leptin receptor signaling also governs reproductive function, immune modulation, bone formation, and glucose metabolism[12]. The blockade of LEPR signaling, thus, can inevitably result in the triad of infertility, immune dysfunction, and compromised insulin sensitivity. These pleiotropic effects underscore the leverage of the leptin-LEPR axis on human physiology as well as disease pathogenesis[13].

Given the intricacy of obesity and its escalating prevalence globally, it is imperative to incorporate genetic, molecular, and environmental data to draw a clear picture of its multifactorial nature. Despite the fact that lifestyle modification is still the mainstay of obesity management, the limited success of it in the long run calls for the need to investigate molecular targets such as LEPR. The latest advances in genome-wide association studies (GWAS), functional genomics, and precision medicine strategies have led to the discovery of LEPR variants with possible clinical application in risk prediction, therapeutic response, and drug development [14].

1.1. Rationale for the Review

Basically, the reasons for conducting the review can be summarized in 3 major issues: First of all, leptin resistance and receptor mutations still pose a challenge to researchers and it is very difficult to pinpoint exactly the mechanisms that are involved. Also, the studies on LEPR polymorphisms are very few, and the results obtained have not been that consistent, neither in terms of the ethnicities examined nor with regard to the different methodologies. Lastly, very little translational research has been done to connect genetic findings with clinical applications. A thorough review of the literature can go a long way toward not only clarifying these associations but also delineating the gaps in knowledge and charting the course for future investigations of precision obesity management [15,16].

1.2. Objectives of the Review

The goal of this paper is to review the scientific literature regarding the leptin receptor gene and the origin of obesity and subsequently:

1. Description of the molecular structure of the gene, isoforms, and how the LEPR gene functions.

2. Present the key polymorphisms of LEPR and the associations of these polymorphisms with obesity as well as metabolic traits in diverse populations.

3. Identifying the pathological mechanisms that connect LEPR malfunction with the development of leptin resistance and changes in energy balance.

4. Listing the implications of therapy and the next steps in research for using LEPR signaling as a target in obesity treatment.

Collaboratively with this narrative synthesis, the article aims at expanding the understanding of the relationship between genetic variations in the leptin receptor and obesity pathogenesis and acknowledging the role of LEPR potential as a biomarker and therapeutic target in the era of precision medicine.

2. Structure and Function of the Leptin Receptor Gene

Essentially, leptin receptor is the one that recognizes and merges the biological signals of leptin, the hormone produced by fat cells that control appetite, energy expenditure, and metabolic balance, into the body. LEPR gene codes for a class I cytokine receptor which is structurally and functionally similar to the receptors for interleukins and Growth Hormone. Knowledge of its gene layout, isoforms, and signaling domains sheds light on the mechanism by which leptin signaling influences body functions and the way its impairment results in obesity [17].

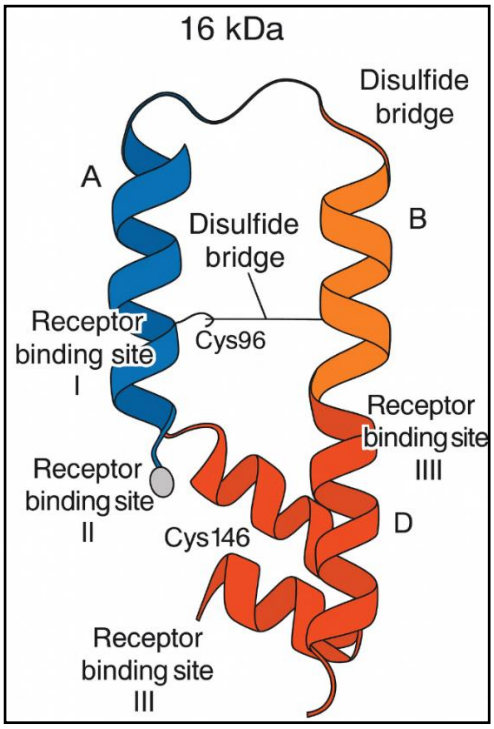


Figure 1. Structural organization of the leptin protein.

2.1. Gene Location and Isoforms

The LEPR gene in humans is situated on the short arm of chromosome 1 (1p31). It covers area of about 70 kilobases (kb) and has 20 coding exons separated by intronic sequences. The gene has a closely similar structure to other mammalian species which indicates the evolutionary significance of leptin signaling in energy homeostasis [18]. The promoter region of the LEPR gene has many regulatory elements including the binding sites for transcription factors like STAT3, C/EBP, Sp1, and PPARγ that regulate not only the expression of tissue and level but also the response of these tissues to hormonal and nutritional stimuli. Besides, epigenetic mechanisms such as DNA methylation and histone acetylation are involved in the regulation of LEPR

gene transcriptions especially by dietary and environmental factors [19].

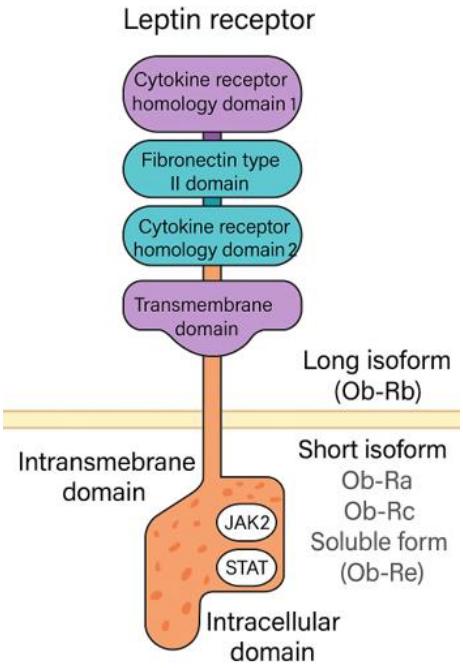
Alternative splicing of LEPR mRNA leads to the generation of different isoforms of the leptin receptor which are labeled as Ob-Ra, Ob-Rb, Ob-Rc, Ob-Rd, Ob-Re, and Ob-Rf. These isoforms have a similar extracellular ligand-binding domain and a transmembrane segment, but the differences between them are substantial in terms of the length and the types of the intracellular domains which eventually result in the functional diversity of leptin signaling and receptor trafficking [20]. The long isoform (Ob-Rb) is the one which is the most abundantly expressed in the hypothalamus, particularly in the arcuate nucleus of the ventromedial nucleus and the dorsomedial nucleus. It is also the full-length, signaling-competent receptor. The Ob-Rb receptor contains all the intracellular motifs required for the binding and subsequent activation of intracellular signaling from the JAK-STAT pathway. The binding of leptin to the receptor and the subsequent activation of the JAK-STAT pathway is considered to be the mechanism by which leptin mediates its anorexigenic and thermogenic effects [21].

On the other hand, the short isoforms (Ob-Ra, Ob-Rc, Ob-Rd, and Ob-Rf) have only the short fragments of the cytoplasmic tails and thus lack the full signaling domains, but they still perform the necessary functions of leptin transport, clearance, and signaling in the peripheral areas. As an example, Ob-Ra is a protein that is found in a variety of tissues that areliberally supplied by blood such as the lung, kidney, and choroid plexus and one of its major functions is thought to be the transport of leptin from the blood to the brain across the blood–brain barrier (BBB) [22]. This is the only way that leptin, a hormone that is released by adipocytes, and is present in the blood in a relatively high concentration, can reach hypothalamic neurons so that it can be of physiological use. The soluble form of the receptor, Ob-Re, is a product of the proteolytic cleavage of the extracellular domain or alternative splicing and is a plasma protein that binds to leptin. It regulates the bioavailability and stability of leptin by both inhibiting its degradation and also by regulating the levels of free leptin in the blood [23].

Isoform	Structure (aa length)	Tissue Distribution	Function
Ob-Ra	~890 aa	Choroid plexus, kidney, lung	Transport of leptin across BBB
Ob-Rb	~1162 aa	Hypothalamus, adipose tissue	Full signaling via JAK2–STAT3, MAPK
Ob-Rc	~894 aa	Lung, kidney	Secondary signaling, leptin clearance
Ob-Rd	~891 aa	Peripheral tissues	Truncated isoform; unclear role
Ob-Re	~800 aa (soluble form)	Plasma	Leptin-binding, regulates leptin bioavailability
Ob-Rf	~894 aa	Liver, muscle	Local leptin signaling

Table 1. Overview of Leptin Receptor (LEPR) Isoforms and Their Functions

Diverse isoforms of leptin allow it to have pleiotropic effects in different body tissues. Ob-Rb is the receptor that carries out the usual leptin signaling in the central nervous system, whereas the short forms participate in the regulation of leptin's local effects in the periphery, for instance, in the liver, pancreas, adipose tissue, skeletal muscle, and immune system. The ratio of these isoforms in different tissues and under different physiological states indicates that they have a variety of regulatory functions apart from mediating appetite control.



3.

Figure 2. Structural organization of the leptin receptor (LEPR).

2.2. Receptor Domains and Signaling Capacity

The leptin receptor is structurally a one-time membrane-spanning transmembrane glycoprotein of the class I cytokine receptor family. Three major functional domains make up the mature receptor: the extracellular ligand-binding domain, the transmembrane domain, and the intracellular (cytoplasmic) domain [24].

The extracellular domain which is made of about 800 amino acids is in charge of leptin binding and receptor dimerization. It has two cytokine receptor homology (CRH) domains, an immunoglobulin-like domain, and fibronectin type III-like domains. The CRH2 domain is the main one for leptin binding with high affinity while the CRH1 domain and the Ig-like domain stabilize the receptor structure and help in signal transduction. The structural studies revealed that leptin binding leads to receptor dimerization or conformational change thus the intracellular JAK kinases become active [25].

The protein of the transmembrane domain is made up of 34 hydrophobic amino acids, attaches the receptor to the lipid bilayer of the cell, and allows the receptor to transmit the signal from the outside to the inside of the cell. This domain is not directly involved in the signaling process, but changes or disturbances in this area can have effects on where the receptor is in the cell and its function [26].

The intracellular domain has different structures in different isoforms of the receptor and thus different signaling potential. The long isoform (Ob-Rb) has an intracellular segment of about 300 amino acids which contains three conserved tyrosine residues (Tyr985, Tyr1077, Tyr1138) that are very important for the signaling occurring after the binding event. Once leptin is bound, JAK2 gets activated and the enzyme then modifies these tyrosine residues by adding phosphate groups. This leads to the recruitment of the signaling molecules STAT3, STAT5, and SHP2. The activated STAT3 goes to the nucleus where it regulates transcription of genes involved in appetite (e.g., POMC and NPY), energy expenditure, and glucose metabolism. The Tyr985 site binds to SHP2 thereby connecting leptin signaling to the mitogen-activated protein kinase (MAPK) pathway that governs cell growth and differentiation. Meanwhile, Tyr1138 is the most important residue that helps to activate STAT3 which is the main mediator of leptin's anorexigenic action.

The short isoforms, however, do not have one or more of these tyrosine motifs and hence they are incapable or have very low capability of the JAK–STAT cascade activation. They can, however, start the alternative signaling pathways that involve phosphatidylinositol 3-kinase (PI3K) and AMP-activated protein kinase (AMPK) and thereby lead to peripheral metabolic effects of leptin such as glucose uptake, fatty acid oxidation, and insulin sensitivity modulation [27,28].

Leptin receptor expression is a different matter for various tissues and is controlled by nutritional and hormonal factors. The most considerable expression of Ob-Rb is in the hypothalamus that is mainly in neurons of the arcuate nucleus that produce neuropeptides like proopiomelanocortin (POMC) and neuropeptide Y (NPY) with the former being anorexigenic and the latter orexigenic [29]. Peripheral tissues such as the liver, pancreas, adipose tissue, skeletal muscle, placenta, and immune cells are majorly short receptor isoforms producers. Leptin receptor activation in the liver and adipose tissue modulates lipid metabolism leading to decreased triglyceride accumulation and increased fatty acid oxidation. In β-cells of the pancreas, leptin is the regulator of insulin secretion and glucose homeostasis. In the immune system, LEPR-mediated leptin signaling affects cytokine release, T-cell multiplication, and macrophage implementation, thus binding the energy metabolism with immune responses [30].

The receptor for leptin is a different receptor in terms of its functionality, a multisystem regulator. Its dysfunction in terms of receptor expression, isoform balance, or downstream signaling, results in defective leptin responsiveness, commonly referred to as leptin resistance, which is a characteristic feature of common obesity [31]. Mutation in the gene or the protein or changes in the protein after translation that affect folding, trafficking, or signal transduction may be the reasons for this phenomenon. So, understanding the structure-function relationship of the LEPR gene in detail is a prerequisite for the target therapies that aim at restoring leptin sensitivity and improving metabolic outcomes [32].

3. Leptin Signaling Pathways

Leptin signaling is a prime example of a neuroendocrine system that controls energy and metabolic stability. By binding to the leptin receptor (Ob-R), leptin leads to the activation of various intracellular signaling pathways responsible for coordinating appetite restraint, heat production, and glucose–lipid metabolism [33].

It is the Janus kinase 2 (JAK2)–signal transducer and activator of transcription 3 (STAT3) pathway that mainly transmits leptin's anorexigenic effects. Other less-significant pathways, such as mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K), support leptin's diverse functions in peripheral metabolism,

reproduction, and immune system regulation. At the same time, antagonists to the cytokine signaling such as suppressor of cytokine signaling 3 (SOCS3) and protein tyrosine phosphatase 1B (PTP1B) that regulate receptor sensitivity are also involved in the occurrence of leptin resistance.

Moreover, leptin signaling gets integrated with insulin and inflammatory pathways, thereby becoming the central player in metabolic regulation and systemic energy balance [34].

Pathway	Key Molecules	Major Function	Impact of LEPR Mutation	Outcome
JAK2–STAT3	JAK2, STAT3	Appetite suppression, energy homeostasis	Reduced STAT3 activation	Hyperphagia, obesity
MAPK	ERK1/2, SHP2	Cell proliferation, metabolism	Impaired ERK activation	Insulin resistance
PI3K–AKT	IRS, PI3K, AKT	Glucose uptake, lipid regulation	Attenuated AKT signaling	Dyslipidemia, T2DM
AMPK	AMPKα, ACC	Fat oxidation, energy sensing	Inhibited AMPK	Reduced energy expenditure

Table 2: Key LEPR Signaling Pathways and Their Biological Effects

3. `JAK2–STAT3 Pathway: The Main Mediator of Leptin Effect

The JAK2–STAT3 pathway is the main signaling pathway that leptin uses to regulate energy homeostasis in the central nervous system. When leptin binds to the long form of the leptin receptor (Ob-Rb), the receptor molecules come together, which leads to the activation of JAK2, a tyrosine kinase of the cytoplasm that is always bound to the intracellular part of LEPR. JAK2 that is activated will phosphorylate itself and after that, it will phosphorylate the receptor on three tyrosine residues in the cytoplasmic tail: Tyr985, Tyr1077, and Tyr1138 [35].

Out of these, the most important tyrosine residue for the interaction of leptin receptor with STAT3 is Tyr1138 the one that is responsible for the recruitment and activation of STAT3, the main downstream mediator of leptin signaling. Phosphorylated STAT3 can form homo- or heterodimers that are transported to the nucleus and bind to the specific areas of promoter regions of the target genes to activate or repress their transcription. One of the genes that are transcribed as a result of STAT3 activation is proopiomelanocortin (POMC), a precursor of α-melanocyte-stimulating hormone (α-MSH), which exerts its function via binding to melanocortin-4 receptors (MC4R) in the hypothalamus leading to appetite suppression. Also, STAT3 signaling causes the reduction of neuropeptide Y (NPY) and agouti-related peptide (AgRP) mRNA levels that are orexigenic neuropeptides - i.e. they promote feeding behavior. These two processes allow leptin to cut down on food intake and to enhance energy usage [36,37].

The JAK2–STAT3 pathway is also involved in mediating leptin effects on glucose and lipid metabolism that are peripheral. Leptin in hepatocytes and skeletal muscle, on the other hand, activates STAT3-dependent transcription of genes related to fatty acid oxidation, mitochondrial biogenesis, and insulin sensitivity, thus metabolic efficiency is enhanced. In addition, the JAK2–STAT3 cascade is not working in isolation but rather must be considered together with the other metabolic regulators such as AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptors (PPARs), since they form a network to maintain systemic energy balance [38].

If the JAK2–STAT3 pathway is thwarted by receptor mutations, phosphorylation impairment or resistance to signaling that is downstream of the receptor, the result is leptin unresponsiveness manifesting as hyperphagia, obesity, and metabolic dysregulation. Therefore, this pathway is the foundation of leptin biology and offers a hurdle to be overcome therapeutically in metabolic diseases [39].

3.2. MAPK and PI3K Pathways: Additional Communication Signals

Aside from JAK2–STAT3 pathway that is primarily responsible for leptin anorexigenic and thermogenic effects, the hormone may also stimulate other different noncanonical pathways such as MAPK and PI3K, which are responsible for its wider biological effects [40].

3.2.1. MAPK Pathway

One of the events leading to the initiation of the mitogen-activated protein kinase (MAPK) pathway, in particular, the extracellular signal-regulated kinase (ERK1/2) cascade, is the binding of leptin that induces phosphorylation of Tyr985

in the LEPR cytoplasmic domain. This is the site where the phosphatase Src homology 2 (SHP2) binds, which with the help of growth factor receptor-bound protein 2 (Grb2) and son of sevenless (SOS), forms the complex that activates Ras and ultimately leads to the phosphorylation of ERK1/2.Phosphorylated ERK moves to the nucleus and interacts with c-Fos, Elk-1, and CREB transcription factors, thereby influencing gene expression for cell proliferation, differentiation, and synaptic plasticity. The MAPK pathway plays a role in the hypothalamus by facilitating neuronal remodeling and could be involved in the regulation of energy balance and leptin sensitivity over a longer period of time. Outside the brain, it modulates fat metabolism, glucose uptake, and insulin signaling [41,42].

3.2.2. PI3K Pathway

The phosphatidylinositol 3-kinase (PI3K) pathway is one of the crucial ways that leptin changes metabolic metabolism. An activation of JAK2 thus recruits insulin receptor substrate (IRS)-1 and IRS-2 that stimulate PI3K to produce phosphatidylinositol (3,4,5)-trisphosphate (PIP3). PIP3 binds and activates protein kinase B (Akt) that regulates cellular survival, glucose uptake, and insulin sensitivity.

The PI3K–Akt pathway in hypothalamic neurons is responsible for rapid, non-genomic effects of leptin, such as the modulation of ATP-sensitive potassium (KATP) channels that determine neuronal excitability. This pathway in adipose and hepatic tissues triggers the oxidation of fatty acids and the inhibition of lipogenesis, thus contributing to lipid homeostasis [43].

MAPK and PI3K pathways supplement JAK2–STAT3 ones in leptin-driven immediate as well as long-term regulation of energy balance and metabolic adaptation.

3.3. Negative Feedback Regulation: SOCS3 and PTP1B in Leptin Resistance

Leptin signaling is governed by negative feedback mechanisms in order to prevent overstimulation and maintain homeostasis. Two major inhibitor sets suppressor of cytokine signaling 3 (SOCS3) and protein tyrosine phosphatase 1B (PTP1B) are the major intrinsic brakes that leptin receptor activity is subjected to (44).

SOCS3 that is a STAT3-inducible protein, interacts with phosphorylated Tyr985 on the LEPR cytoplasmic tail thus hindering JAK2 and STAT3 access to the receptor. Consequently, this is the point at which the signaling cascade is halted and the receptor enters a desensitized state.

During obesity, a chronic hyperleptinemia situation results in a long-lasting induction of SOCS3 in hypothalamic neurons which is the main reason for a continuous blockade of leptin signaling that in turn leads to the state of leptin resistance - a major cause of impaired hypothalamic leptin signaling (45).

Contrarily, PTP1B is a cytoplasmic phosphatase that removes phosphoryl groups from JAK2 and other tyrosine-phosphorylated intermediates leading to the termination of leptin signaling. High levels of PTP1B expression, especially in the hypothalamus and liver, have been very tightly linked to the condition of leptin insensitivity and obesity.

Elimination of the PTP1B gene in rodents not only increases leptin response but also makes the animals less prone to obesity caused by high-fat diet, thus, giving rise to its potential as a therapeutical target if turned into a drug position [46].

Both SOCS3 and PTP1B are good examples of the necessity for signaling activation and inhibition to be in equilibrium for metabolic stability to be maintained. These feedback elements' misregulation leads to a prolonged situation of leptin insensitivity which is caused by an endless cycle of food overconsumption and weight gain although there are high levels of leptin in circulation (47).

3.4. Cross-Talk with Insulin and Inflammatory Pathways

Leptin signaling is interconnected with insulin and inflammatory routes to form a network that determines energy metabolism, glucose regulation, and immune responses.

On a single-molecule scale, leptin and insulin operate through shared downstream mediators that involve IRS–PI3K–Akt signaling, thereby leading to simultaneous regulation of glucose uptake and lipid metabolism. In hypothalamic neurons, leptin stimulates the insulin anorexigenic effects, whereas in peripheral tissues it acts as insulin sensitizer by bringing about fatty acid oxidation and lessening of the ectopic lipid deposition. However, the good interaction between these two hormones could be broken by chronic inflammation and nutrient overload [48].

One of such factors as proinflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) initiate cell signaling events (particularly IKKβ/NF-κB and JNK) that lead to decrease in leptin and insulin receptor phosphorylation. Consequently, this state of cross-inhibition is related to central and peripheral leptin resistance and is the main reason coupling of obesity, insulin resistance, and type 2 diabetes. Besides this, leptin by itself is doing immune modulation through triggering macrophages and T lymphocytes via JAK–STAT and PI3K pathways, thus, there is a bidirectional link between metabolism and immunity[49].

4. Genetic Variants of the LEPR Gene

4.1. Common Polymorphisms

The LEPR gene on chromosome 1p31 is a very polymorphic gene and has a few single nucleotide polymorphisms (SNPs) that alter receptor function and downstream leptin signaling. Out of these, Q223R (rs1137101), K109R (rs1137100), and K656N (rs8179183) are the most talked-about variants, as they are the most biologically relevant ones in obesity and its associated metabolic abnormalities [49].

The Q223R polymorphism is a case of adenine (A) to guanine (G) substitution in exon 6. This amino acid change from glutamine to arginine can change both receptor affinity and signaling efficiency. The R allele carriers are often reported to have higher leptin levels in serum and greater body fat, a condition known as leptin resistance. Likewise, K109R in exon 4 changes the lysine to arginine, thus possibly influencing the receptor's extracellular domain that is involved in leptin binding. The K656N polymorphism in exon 14 changes the intracellular signaling domain, thus it can affect JAK2-STAT3 pathway activation [50].

SNP ID	Amino Acid Change	Population	Effect on Receptor	Association with Obesity/Metabolic Traits
rs1137101 (Q223R)	Glutamine → Arginine	Global	Alters extracellular domain binding	↑ BMI, leptin resistance
rs1137100 (K109R)	Lysine → Arginine	Asian, European	Impairs leptin binding	↑ Waist circumference
rs8179183 (K656N)	Lysine → Asparagine	Caucasian	Affects receptor signaling	↑ Risk of T2DM and obesity
rs1805134	Silent variant	Indian	No amino acid change	Neutral or mild risk

Table 3: Major LEPR Gene Polymorphisms and Their Association with Obesity

Moreover, polymorphisms to watch out for are rs1805094, rs8179183, and rs13306519, which may have an impact on body composition, insulin sensitivity, and lipid metabolism. The overall impact of these gene polymorphisms is generally specific to certain populations, where differences in allelic frequency between Asian, European, and African groups have been observed, indicating a variation in obesity predisposition among different ethnic groups [51].

3.2. Population-Based Association Studies

Numerous case–control and cohort studies of diverse populations worldwide have revealed associations of LEPR variations with body mass index (BMI), adiposity, serum leptin levels, lipid profile, and insulin resistance. A good example is the Q223R polymorphism, which has been in Indian and East Asian populations that exhibit association with increased BMI, waist circumference, and hyperleptinemia. On the other hand, some European cohorts have suggested that there is less or no association, thus environmental and dietary factors may influence genetic risk [52].

The research involving adults in Mexico showed that the people with the R allele of Q223R had higher triglyceride levels and insulin resistance indices, which is a way of telling that LEPR variants might be the cause of energy metabolism dysregulation. According to a similar trend for the Chinese Han populations, the presence of K109R and K656N was associated with the components of metabolic syndrome such as high fasting glucose and decreased HDL cholesterol. These associations highlight the multifactorial role of LEPR polymorphisms in obesity and its metabolic sequelae [53].

3.3. Meta-Analyses and Genome-Wide Association Studies (GWAS)

Ethnicities have been the focus of data across which several meta-analyses have gathered evidence in support of the significant contribution of LEPR variations to obesity risk. It was found in a meta-analysis with more than 25,000 participants that there was a substantial association between rs1137101 (Q223R) and BMI increment with a dominant effect in Asian and Latin American populations. Another study characterized the co-existence of both Q223R and K109R variants to be associated with higher leptin and insulin levels and thus, considered as a possible cause of leptin resistance [54].

LEPR loci have been reported as one of the obesity-related regions in the largest cohorts conducted by UK Biobank & GIANT consortium through genome-wide association studies. Nevertheless, the impact of the regions is quite low reflecting polygenic inheritance and gene-environment interaction. What's more, ethnic differences have unfolded with Q223R posing a greater risk to Asians while K109R is more indicative in European populations. Thus, these clues reinforce the necessity of amalgamating data from genomics, transcriptomics along with the environment factors to unravel LEPR's role in obesity [55].

3.4. Epigenetic Modifications and LEPR Expression

Besides variations in the DNA sequence, epigenetic mechanisms significantly influence LEPR expression. Methylation in the promoter region can inhibit LEPR transcription in both adipose and hypothalamic tissues, thus resulting in leptin resistance. Researchers have demonstrated that the obese individuals with LEPR hypermethylation show a strong correlation between that modification and a reduction in receptor mRNA as well as defective leptin signaling [56].

Moreover, microRNAs (miRNAs) such as miR-27a, miR-200a, and miR-519d, which are involved to post-transcriptional modulation of LEPR translation, also participate in this process. These miRNAs' expressions are generally increased in obesity and they negatively correlate with the receptor protein levels. Besides that, factors in the environment like a diet rich in fat, lack of physical activity, and exposure to endocrine disruptors–may still increase the extent of these epigenetic changes. Therefore, the LEPR malfunction is not only a matter of interplay between genetic predisposition and environmental factors, but it also represents the very junction where the two come together [57].

4. Leptin Resistance in Obesity

4.1. Mechanisms of Leptin Resistance

One of the features of common obesity is leptin resistance, which is characterized by high levels of leptin in the blood together with a low response from the brain. Various mechanisms have been proposed to explain the interaction of the different parts of the body that lead to impaired leptin sensitivity:

a) Transport Across the Blood–Brain Barrier (BBB) Is Impaired: The CNS needs leptin, which it gets through a transport process that can be saturated. In obesity, this process becomes less efficient so that even with high leptin levels, the access of the hypothalamus is limited.

b) Signaling From the Receptor Is Defective: Changes, or polymorphisms in LEPR, may alter receptor sensitivity or interfere with JAK2-STAT3 activation. Long-lasting high levels of leptin may cause the receptor to be less active as a consequence of internalization or downregulation of Ob-Rb desensitizing the receptor signaling.

c) Inflammation and Endoplasmic Reticulum Stress: Obesity-related inflammation leads to activation of suppressor proteins such as SOCS3 and PTP1B that block LEPR signal transduction. ER stress that is present in the obese adipose tissue also causes the leptin receptor to be misfolded and it cannot be easily transported.

These pathways combine to lessen anorexigenic signaling, thus resulting in a positive energy balance and further weight gain [58,59,60].

4.2. Role of LEPR Mutations

While common variants only influence the risk, very rare homozygous or compound heterozygous mutations in LEPR lead to severe early-onset monogenic obesity. These changes result in truncated or nonfunctional leptin receptors that lack the ability to bind leptin or activate JAK2. The symptoms of such patients include hyperphagia, rapid weight gain from early life, hypogonadotropic hypogonadism, and immune system abnormalities.

Over fifty different pathogenic mutations have been identified, which include missense, nonsense, and frameshift mutations. Functional experiments show that these mutations make STAT3 phosphorylation and transcriptional activation of the anorexic genes such as POMC impossible. People with LEPR deficiency are usually seared with very high leptin levels that point out the receptor's vital role in the feedback regulation [61,62].

4.3. Clinical and Biochemical Correlations

Leptin levels in serum are mostly reflective of body fat mass; however, receptor function is what determines biological responsiveness. Obese people may have an elevated leptin level, yet a reduced hypothalamic signaling which is a sign of functional leptin resistance is usually detected. In contrast, slim people with functional LEPR signaling can maintain energy equilibrium even at lower leptin levels.

Clinical correlations provide evidence that polymorphisms such as Q223R are related to changes in the leptin-BMI relationship and also to a higher risk of insulin resistance. These findings emphasize that obesity is not only due to excessive leptin production but also to the failure of receptor-mediated feedback [63].

5. LEPR Gene and Associated Metabolic Disorders

The malfunction of the leptin receptor that causes energy imbalance mostly by adiposity regulation, but, however, leads to abnormal metabolic homeostasis that is typical of various metabolic diseases.

- Type 2 Diabetes Mellitus (T2DM): Genetic variants of LEPR result in the development of insulin resistance through the mechanisms such as the loss of hypothalamic control over glucose metabolism and the reduced insulin sensitivity of the peripheral tissues. Hyperleptinemia coupled

with decreased receptor responsiveness is conducive to the development of hyperinsulinemia and β-cell stress.

- **Metabolic Syndrome:** Polymorphisms like Q223R and K109R that are associated with attributes of metabolic syndrome such as central obesity, dyslipidemia, hypertension, and glucose intolerance cluster thus constituting metabolic syndrome. Raised levels of leptin are both indicators and facilitators of this syndrome.
- **Non-Alcoholic Fatty Liver Disease (NAFLD):** The lack of leptin signaling contributes to the development of liver steatosis by changing lipid oxidation that is accompanied by inflammation. The LEPR in the liver cells regulates AMPK activity and the metabolism of fatty acids; therefore, a reduction in receptor function makes NAFLD more likely.
- **Polycystic Ovary Syndrome (PCOS):** LEPR polymorphisms have been linked to manifestations such as hyperandrogenism, insulin resistance, and irregularity of the ovulatory cycle. Leptin is a component of the reproductive neuroendocrine system, and the impairment of this signaling pathway is one of the causes of the PCOS pathophysiological mechanism.
- **Cardiovascular Risk Markers:** Leptin resistance leads to the release of mediators such as pro-inflammatory cytokines which in turn cause endothelial dysfunction thus leading to cardiovascular diseases. Moreover, leptin resistance is accompanied by altered lipid metabolism that contributes to the increase of cardiovascular risk. The most common findings in individuals with LEPR variants are elevated C-reactive protein (CRP) and reduced HDL cholesterol.

Collectively, these findings underscore that LEPR gene dysfunction is not confined to adiposity but represents a nexus connecting obesity to systemic metabolic derangements [64,65,66].

6. Therapeutic Implications

6.1. Pharmacogenomic Perspectives

Pharmacogenomics has been evolving at a rapid pace and has already uncovered the fact that variations in the LEPR gene affect the response to anti-obesity drugs. The knowledge of the molecular mechanisms of obesity is fundamental to the rise of personalized obesity therapy.

Researchers have found that patients with different polymorphic forms of the LEPR gene such as Q223R (rs1137101) and K109R (rs1137100) not only have distinct reactions to weight loss drugs but also to metabolic modulators [67]. To illustrate, an individual with the R allele at the Q223R position of the LEPR gene may be less sensitive to leptin therapy and hence experience a lower impact of lifestyle changes, most likely as a result of dysfunctional receptor-mediated signaling. Moreover, these variants have been linked to changes in the response to GLP-1 receptor agonists like liraglutide and semaglutide, which are drugs that share several pathways with leptin in the hypothalamus, e.g. JAK2–STAT3 and PI3K–Akt cascades [68].

Therefore, pharmacogenomic testing may facilitate the tailoring of the medication, the dose adjustment, and the therapeutic combinations by detecting LEPR genotypes that correspond to positive results. Not only does this precision-guided intervention increase the effectiveness of the treatment, but also the risk of treatment failure and the cost of the therapy are lowered. LEPR genotyping integration in clinical procedures might be especially useful in communities where obesity is widespread and there is a significant genetic diversity, e.g. South Asians [69].

Approach	Mechanism	Therapeutic Agent/Method	Clinical Status	Challenges
Leptin analogs	Leptin replacement	Metreleptin	FDA-approved for lipodystrophy	Limited efficacy in common obesity
LEPR sensitizers	Enhance receptor activity	GLP-1 analogs, amylin co-therapy	Phase II/III	Receptor resistance
Gene therapy	Correct LEPR mutations	CRISPR-Cas9 editing	Preclinical	Off-target effects
RNA therapeutics	Modulate LEPR expression	siRNA, mRNA delivery	Experimental	Delivery challenges
Nanocarrier delivery	Targeted leptin delivery	PEGylated liposomes, nanoparticles	Preclinical	Bioavailability issues

Table 4: Potential Therapeutic Approaches Targeting LEPR Dysfunction

6.2. Leptin-Based Therapies

After leptin was identified in 1994, the use of externally supplied leptin was at first considered a possible solution to obesity. However, later on, experiments showed that leptin alone, such as the recombinant analog metreleptin, is generally not effective in people with common obesity, as the problem is leptin resistance rather than leptin deficiency.

In patients with congenital leptin deficiency or generalized lipodystrophy, where the absence of endogenous leptin causes severe metabolic disorders, metreleptin, a human leptin analog, brought about significant improvements. In these rare situations, the therapy helped to normalize appetite, glucose metabolism, and lipid levels. However, in people with increased endogenous leptin levels and impaired LEPR signaling, metreleptin was not able to bring about a notable reduction in body weight [70].

There have been attempts to use combination methods to counteract leptin resistance. The joint administration of leptin and amylin analogs (pramlintide) or GLP-1 agonists has resulted in synergistic effects in enhancing satiety and consequently, small weight loss. But these results are short-lived, and the issue of finding leptin sensitizers that can either restore receptor signaling or facilitate BBB transport still dominates the field.

6.3. Novel Interventions

Because of the ineffectiveness of standard treatments, novel interventions that target LEPR function are being considered.

a) Gene Therapy: Gene replacement methods are designed to reverse LEPR mutations that cause disease by using viral or non-viral vectors. Animal studies on LEPR-deficient mice have shown that the delivery of the gene to the hypothalamus not only restores leptin sensitivity but also brings body weight back to normal. However, before such an approach can be used in humans, there are issues related to safety, immune response, and the accuracy of delivery that need to be resolved.

b) CRISPR/Cas9 Gene Editing: Accurate genome editing is one of the options for fixing the problematic LEPR mutations at the DNA level. One instance of CRISPR-mediated correction in model organisms led to the improvement of leptin sensitivity and the reduction of fat. The next steps should be focused on uncovering possible off-target effects and dealing with the ethical issues of human application.

c) RNA-Based Therapeutics: Researchers utilize small interfering RNAs (siRNAs) and antisense oligonucleotides (ASOs) that target the negative regulation of leptin signaling caused by SOCS3 and PTP1B to enable the LEPR signaling to return to normal. RNA-based interventions allow for the regulation to be reversible and for the specificity to be in a certain tissue, which makes these interventions very promising as obesity therapy partners.

d) Combination Approaches: The most effective way might be a comprehensive plan that incorporates lifestyle changes (diet, exercise) along with medication and genotype-guided interventions. Using LEPR status in treatment algorithms can make weights of caloric restriction, exercise programs, and pharmacological adjuncts individualized.

Together, these groundbreaking measures highlight the potential of LEPR-targeted treatments to move the issue of obesity from general management to interventions of a highly personalized nature [71,72,73].

7. Future Directions

Leptin and its interaction with the LEPR complex inherently is biologically complex, therefore our research must not only contemplate this but also continuously integrate new insights at the molecular, clinical, and population levels.

7.1. Integration of Multi-Omics Approaches

Resolving leptin resistance down to molecular mechanisms should be supported by the involvement of layers like genomics, transcriptomics, proteomics, epigenomics, and metabolomics. Adopting such multi-omics approaches opens up new possibilities for locating key molecular nodes that connect LEPR malfunction with the systemic metabolic changes. The use of modern bioinformatics and systems biology methods can provide a detailed picture of the interplay between these molecules and also allow for testing how signaling pathways respond to different disease states.

As an illustration, proteomic experiments may surface changes in STAT3 phosphorylation or SOCS3 expression subsequent to the LEPR signaling while metabolomic characterization can map changes in lipids and amino acids linked to LEPR variants. Such integrative omics data pave the way of our therapeutic designs more effectively and also enable a more accurate estimate of outcomes [74,75].

7.2. Personalized Obesity Medicine

Obesity medicine based on personalized interventions rather than population-wide measures is just around the corner. LEPR genotyping combined with clinical data (BMI, leptin levels, metabolic markers) can be a tool for prediction of risk, early diagnosis, and customized treatment application.

Next-generation AI-based predictive models employing genetic and lifestyle information can be an interactive solution for intervention personalization [76].

The precision in drug administration especially for leptin analogs, incretin mimetics, or anti-inflammatory agents, through pharmacogenomics, can entirely change the scenario enhancing the success rate and reducing side-effects.

7.3. Population-Specific Genetic Profiling

Differences in the distribution of LEPR polymorphisms among various ethnicities imply that genetic profiling should be tailored to populations. Up till now, most of the genome-wide association studies have primarily focused on the European population, thus there are data shortages for South Asian, African, and Native populations, which are already under the double burden of obesity and metabolic diseases.

Creating local LEPR allele frequency reference panels and using them for developing health policies will contribute to leveling up the playing field in obesity research and management worldwide [77.78].

8. Research Gaps

In spite of an exhaustive volume of literature, the following knowledge gaps remain prominently:

- **Longitudinal Studies:** The majority of studies have a cross-sectional design, and it is therefore unclear how long-term studies monitoring leptin dynamics, receptor activity, and lifestyle interaction would unfold.
- **Multi-Ethnic Data:** Our knowledge of the impact of LEPR variations on obesity risk across different ethnic genetic backgrounds is still insufficient.
- **Functional Validation:** There is a scarcity of experimental evidence linking the identified SNPs to changes in receptor functionality.
- **Therapeutic Translation:** The scope and diversity of clinical trials aimed at LEPR signaling are still limited.

To close these gaps, we need cross-talk between genomics, endocrinology, and bioinformatics disciplines and a concerted effort to revise leptin biology concepts [79,80].

Area	Current Limitation	Research Need	Potential Impact
Genetic studies	Limited ethnic diversity	Multi-ethnic GWAS	Broader understanding of LEPR variants
Epigenetic regulation	Few longitudinal studies	Time-course methylation analysis	Dynamic insight into leptin resistance
Therapeutics	Lack of LEPR-specific drugs	High-throughput screening for sensitizers	Personalized obesity treatment
Systems biology	Poor integration of omics	Multi-omics modeling (genomics, metabolomics)	Holistic obesity pathway mapping

Table 5: Knowledge Gaps and Future Research Directions

Bridging these gaps will require interdisciplinary collaboration across genomics, endocrinology, and bioinformatics to refine our understanding of leptin biology [79,80].

Conclusion

The leptin receptor gene is a core molecular controller of appetite regulation, energy consumption, and metabolic balance. Genetic polymorphisms, most notably Q223R, K109R, and K656N, alter the leptin signal transduction to a significant extent and are the main contributors to differences in obesity susceptibility among individuals. The failure of LEPR signaling, in a case of mutations, epigenetic silencing, or inflammation-induced inhibition, is the cause of leptin resistance which is the feature of common obesity. This impairment of regulation not only causes the excessive fat storage but also establishes the link between obesity and metabolic diseases such as type 2 diabetes, metabolic syndrome, PCOS, and cardiovascular disease.

Despite the major progress in variant identification of LEPR, the implementation of these genetic hints to deliver effective clinical interventions is still quite a challenge. Typical treatments are often unsuccessful because of receptor-level resistance which is the reason why a revolutionary approach like gene therapy, CRISPR-based correction, RNA therapeutics, or pharmacogenomic-guided treatments is required.

In the future, the management of obesity will need to follow a precision medicine model that incorporates the analysis of multi-omic data, LEPR genotyping, and personalized therapeutic modulation. The comprehensive insight into LEPR interactions with metabolic and inflammatory

pathways will give us a ticket to explore new treatment options, thus allowing us to offer bespoke therapies targeting leptin resistance and getting better follow-up results. Consequently, the LEPR-focused strategy is a potential coming frontier that could respond to the global obesity crisis at the intersection of genetic and molecular precision.

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