Review Article

Decoding Leptin: Unraveling the Role of Leptin Signaling in the Battle against Obesity

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ABSTRACT

Obesity represents a major global health crisis, linked to a spectrum of metabolic disorders, including diabetes, cardiovascular diseases, and hypertension. Leptin, a hormone predominantly produced by adipose tissue, plays a critical role in regulating energy balance, appetite, and metabolism. Historically, leptin was believed to be a cornerstone in the management of obesity due to its ability to suppress appetite. However, the effectiveness of leptin therapy has been limited by the phenomenon of leptin resistance in obese individuals. This review, titled "Decoding Leptin: Unraveling the Role of Leptin Signaling in the Battle Against Obesity," aims to delve into the molecular intricacies of leptin signaling pathways and their implications in obesity management. We explore the mechanisms underlying leptin resistance, the impact of leptin on neuroendocrine pathways, and the potential for resetting leptin sensitivity as a therapeutic strategy. Additionally, we discuss recent advances in therapeutic approaches aiming to enhance leptin sensitivity or mimic its effects, including novel pharmacological agents and lifestyle modifications that influence leptin signaling. By providing a comprehensive overview of current research and emerging therapies, this review seeks to illuminate the path forward in leveraging leptin signaling for more effective obesity interventions.

Key words: Leptin Resistance, Obesity Management, Therapeutic Strategies, Neuroendocrine Regulation

Obesity can be defined as a condition which can be characterized by excessive accumulation of body fat which has the capability to show negative impact of health, in general a person could be said that he or she is suffering from obesity by checking the BMI over 30 kg/m^3[1]. There are Certain East Asian Countries they apply lower value for defining the obese condition. Obesity can be linked with various other health risk factors, such as cardiovascular diseases, Type II Diabetes, Obstructive sleep apnea, certain cancers, osteoarthritis, obesity can also be influenced by a reciprocal relationship by depression.

Obese condition for children ranging between the age of 5-19, can be defined with the BMI with two standard deviations above the median their age group [2], and for the age group below the age of 5, the obese condition is considered to be the three-standard deviation above the median. The assessment of fat distribution and cardiovascular risk factorcould be done by subdividing BMI by the CDC [3]. When it comes to the etiological factors of obesity, excessive calorie intake and leading a sedentary life plays major role, while the genetics also have some role when it comes to obesity with certain genes showing influence towards susceptibility to obesity [6][9]. In addition, there are certain drug metabolism system which also contributes to the condition of obesity, particularly fat-soluble drugs, like anti-tuberculosis medications [10]. The increase risk of obesity is also accompanied with the treatment for certain physical and mental illness like psychiatric disorder [11]. Finally, the contribution of the hormone leptins plays the vital role in obesity. Leptin is a hormone with helps in regulating the intake of food and energy usage. Obsess condition may occur when the hormone leptin have lost its ability to signal the brain about proper functioning of food intake and usage of energy.

Leptin and its Receptors: Leptin is a neurohormone that acts in the hypothalamus to regulate energy balance and food intake [12]. Recessive mutations in the leptin (obese, ob) or its receptor ObR gene result in profound obesity and type II diabetes mellitus. Further studies demonstrated that in

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addition to its role as a neurohormone, leptin can modulate immune response, fertility, and hematopoiesis, acting as a mitogen, metabolic regulator, or pro angiogenic factor [13]. The central regulation of food intake and energy expenditure is mediated through the binding of leptin to its receptor ObR, a type 1 cytokine receptor. Several isoforms of ObR have been described as a result of alternative mRNA splicing leading to several short isoforms (ObRa, ObRc, ObRd, and ObRf), one long isoform ObRb with a long cytosolic C-terminus tail and one soluble isoform Obre [14].

Hence, ObR isoforms differ in the length of their Intracellular region but share identical extracellular domains. While short isoforms are ubiquitously expressed, ObRb expression is more restricted with high levels in hypothalamic nuclei such as the arcuate nucleus (ARC). The hypothalamic ARC has an important role in the development of leptin resistance. Accordingly, exposure of rodents to a high-fat diet rapidly decreases the phosphorylation of STAT3 in the ARC or the ventral tegmental area (VTA), while leptin-sensitivity is simultaneously maintained in some other hypothalamic nuclei. While the biological function of the short isoforms is still elusive, it is well established that Obftb is the main isoform responsible for the effect of leptin on body weight control. The weight lowering properties of leptin via ObRh has been suggested to be centrally mediated.

Once activated after leptin binding, ObRh is able to trigger various signal transduction pathways. Activation of the Janus tyrosine kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) pathway leads to an increase of anorexigenic signals and a decrease of orexigenic signals [15]. Leptin is also able to activate the insulin receptor substrate (IRS)/phosphatidylinositide 3-kinase (PI3K) pathway, essential for the regulation of glucose homeostasis [16]. Moreover, leptin inhibits the energy 10 sensor adenosine monophosphate activated protein kinase (AMPK) in the brain, to decrease eating. The activation of extracellular signal regulated kinase (ERK) is another pathway mediating the anorectic action of leptin in the hypothalamus.

Leptin Expression In Obesity: Early onset obesities has the capability to form rare genetic mutations which can hamper leptin signaling which might lead to congenital leptin deficiency or leptin resistance. Hyperleptinemia and resistance to reducing body mass is the general characteristics of leptin resistance [5][6][17][18]. A person is leptin resistant, can only be said with the presence of leptin in plasma at higher amount, high amount of leptin in blood plasma certainly corelates with body fat percentage. Several weight loss studies have revealed that the level of leptin can decrease initially and then gradually rise with continued weight loss.

Matheny et al.'s research put light on leptin resistance can be induced in the arcuate nucleus (ARC) and ventral tegmental are (VTA) of the brain with high fat diets, while when it comes to medial basal hypothalamic region it retains sensitivity [20][21]. The critical role of ARC in leptin can be indicated by targeting downregulation of leptin receptor expression in the ARC promoting diet-induced obesity. Activation of SOCS3 and STAT3 resistance to leptin in neuron such as pro-opiomelanocortin (POMC) and AgRP in rodents with high-fat content diet.

While AgRP neurons shows increased sensitivity towards leptin when the rodents are shifted to low-fat content diet. Polymorphism in the crystalline structure of the leptin (ob) and leptin receptor (LEP-R) genes which has the capability to disrupt leptin functions resulting in obesity [22][23][24]. The polymorphism of LEP-2548 G/A are widely studied in humans for understanding obesity. A protein quantitative trait locus (pQTL) analysis study was performed by Carayol et al. to understand the genetic influences on leptin levels and identified FAM46A as the negative signaling regulator in adipose tissue [25][26]. In addition to that distant enhance sequences, LE1 and LepREI, modulate leptin gene expression through PPAR gama/ RXRa binding sites. Noncoding RNAs and epigenetic factors like DNA methylation found in the leptin (ob) and LEP-R genes, are expressions of obesity and leptin insensitivity [27][28].

Mechanisms Underpinning Leptin Resistance: It is worth noting that leptin resistance occurs when there is an impairment of the effectiveness of the ObRb downstream signaling transduction, although in the presence of hyperleptinemia, a lack of anti obesity action of leptin appears. Therefore, leptin resistance is one of the most frequent features in the onset and progression of obesity [29]. This condition is very common in obese humans and occurs after only few weeks of high fat diet (HFD) in rodents. Since the hypothalamus mediates the anti-obesity actions of leptin, three mechanisms are currently accepted to mediate central leptin resistance, such as the reduction in leptin access to CNS through the BBB, the impairment of leptin signaling in first-order neurons expressing ObRb, or in second-order leptin-targeted neurons and neural circuits.

It has been recently suggested that other mechanisms, such as the onset of hypothalamic inflammation, autophagy deficiency or ER stress, can also mediate the obesity-associated central leptin resistance. Indeed, since leptin exerts its biological effects not only in CNS but also in peripheral tissues, parallel to central leptin resistance a peripheral dampening in leptin sensitivity can occur.

Reduction in leptin access to CNS: As it is well-known, ObRa, which is highly expressed by capillary cells of the choroid plexus, actively transports leptin across the BBB to reach the majority of ObRb expressing neurons in the CNS. This transport system is saturable and recently it has been shown to be flanked by another transport mechanism involving the endocytic receptor megalin, as demonstrated by a decrease in leptin cerebrospinal fluid (CSF) levels inmegalin deficiency [30]. In obese individuals the saturation of leptin

transport can occur due to the hyperleptinemia, resulting in an only slightly increase in the CSF leptin levels [31]. Oh-I et al. showed that the impairment of leptin transport across BBB can also be caused by the higher plasmatic levels of cytokines

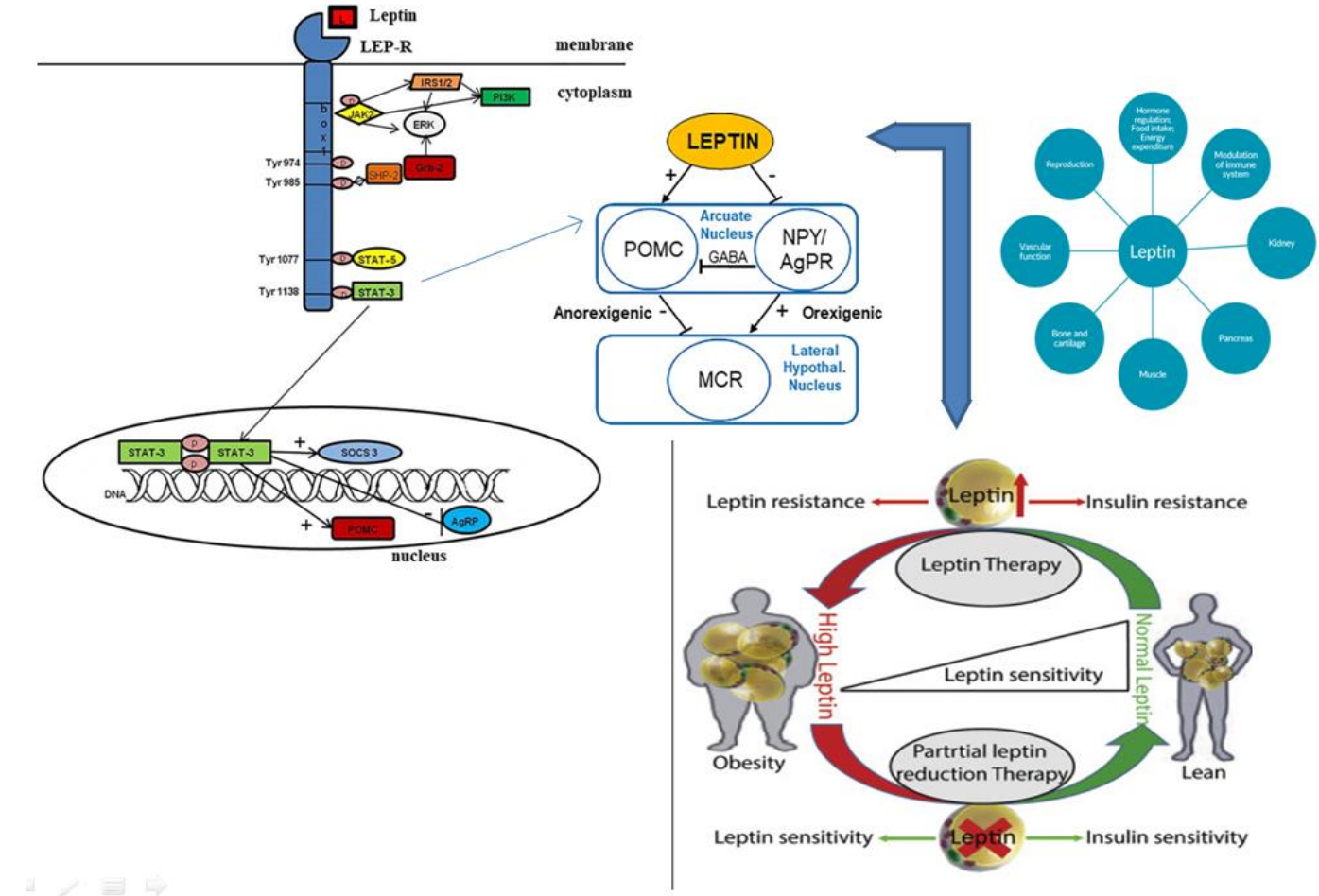

Figure - The pathophysiology of leptin signaling on its crucial role in regulating appetite and maintaining energy balance [52]

and fatty acids in obese individuals relative to lean subjects. To date, it is still unclear the extent to which the impairment of leptin transport to CNS can contribute to the leptin resistance. Indeed, leptin can reach the CNS through the median eminence, which lacks the BBB. Therefore, ARC first-order neurons can sense leptin trough their projections into the median eminence [32].

Impairment of leptin signaling in hypothalamic neurons: Leptin resistance can occur by alterations in each component of the Ob-Rb downstream signaling cascade. In particular, previous findings have highlighted three potential mechanisms: a reduced expression of Ob-Rb at plasma membrane level, an upregulation of negative regulators of leptin signaling, and a downregulation of its positive regulators. Diano et al. have demonstrated that Ob-Rb has a predominant localization in the Golgi apparatus in hypothalamic neuronal and glial cells, thus its trafficking to the plasma membrane is necessary to obtain a physiological response to leptin stimulation. The Ob-Rb expression pattern at cell surface depends on a delicate balance between the activity of the Bardet-Biedl syndrome (BBS) proteins, which mediate its transport to the plasma membrane, and the rate of the ligand independent endocytosis, a process that promotes the Ob-Rb internalization. Regarding the second molecular mechanism underpinning leptin resistance, the Ob-Rb physiological signaling is under control of two negative regulators: SOCS-3 and phosphor tyrosine phosphatase (PTP) 1B [33].

SOCS3 is involved in the onset of leptin resistance at central level, as well as at peripheral level. It has been demonstrated that an increase in SOCS3 mRNA expression is involved in the development of leptin resistance in skeletal muscle from rats on high-fat diet (HFD). Moreover, SOCS3 inhibits AMPK activation in peripheral metabolically active tissues, such the liver, white adipose tissue (WAT) and skeletal muscle, contributing to abnormalities of fatty acid metabolism. AMPK is a fuel-sensing enzyme, whose activity is finely regulated by leptin: in peripheral tissues, i.e. WAT, leptin increases its enzyme activity, promoting the catabolic pathways toward the fatty acid oxidation and glucose internalization, exceeding the anabolism rate.

On the contrary, leptin inhibits AMPK activity at central level, where this enzyme is involved in food intake regulation,

since it controls the release of hypothalamic neuropeptides. In addition to SOCS3, PTP1B is a negative regulator of both leptin and insulin signaling. Leptin resistance is also associated with a downregulation of positive regulators of Ob-Rb signal transduction. In particular, the leptin-induced STAT3 phosphorylation is essential to obtain a clear activation of hypothalamic neurons, releasing thus the anorexigenic neuropeptides.

Impairment of MC4R downstream signal transduction in neural circuits: The melanocortin system controls the energy balance, especially trough the MC4R, which is mostly expressed in the brain. Therefore, alterations in the MCAR-dependent brain-derived neurotrophic factor (BDNF)/Tropomyosin receptor kinase (Trk) B signalling pathway, in the ventromedial nucleus (VMN), can affect leptin resistance. As demonstrated by Liao et al. [34], mice harbouring a truncated long Bdnf 3 UTR develop a severe hyperphagia and a clear obese phenotype. In this genetic model, leptin is unable to activate hypothalamic neurons and reduce food intake.

Role of hypothalamic ER stress in central leptin resistance: The ER is responsible for folding nascent proteins and this process is possible until there is a perfect balance between the ER capability to fold these macromolecules and the amount of loaded proteins. As soon as an imbalance between these folding and loading processes occurs, ER stress appears, leading to the activation of several pathways (ie. unfolded protein response (UPR), inositol-requiring protein (IRE)-1 and protein kinase RNA (PKR)-like kinase (PERK) pathways), which collectively attempt to counteract the ER stress itself, restoring the ER homeostasis.

To date, a growing body of evidence has demonstrated the involvement of the hypothalamic ER stress in central leptin resistance and obesity. Consistently, pharmacological approaches, consisting in the central administration of ER stress inducers or chemical ER chaperons, are able to modulate leptin responsiveness in an opposite manner, identifying a role of ER stress in leptin resistance [35].

Defective autophagy as a contributor of leptin resistance: It has been recently emphasized a key role for the autophagy in regulating the overall energy balance, since the inhibition of this process, by a neuron- specific deletion of autophagy related protein (Atg) 7, can alter the phenotype in mice. In particular, mice show an obese phenotype when this well-known autophagy component is selectively knocked down in POMC neurons, probably because this deletion is associated also with a reduction of leptin- induced STAT3 phosphorylation; in agreement with these results, the deletion of this gene in AgRP neurons causes a reduction in fat mass Collectively, these data highlight that the hypothalamic autophagy deficiency is involved in leptin resistance and obesity [36].

Strategies To Overcome Leptin Resistance:-

Caloric restriction and exercise: Caloric restriction is the first approach for the treatment of obesity able to reduce circulating leptin levels, as an alternative to pharmacologic reversal of leptin resistance. It has been reported that long term exercise, not only decreased leptin levels, but also increases the activation of STAT3 and AMPK signalling pathways in the hypothalamic arcuate nucleus. Prevention of leptin resistance by exercise was also demonstrated by Zhou [37], who showed a reduction in hypothalamic SOCS3 mRNA expression and JAK2/STAT3 signalling pathway in rats fed a high fat diet by exercise. However, when exercise was combined with caloric restriction the effect was more evident compared to those obtained by exercise or diet approach alone [38].

Reversal of the inhibition of SOCS3 and PTP1B: As already depicted, SOCS3 and PTP1B are negative regulator proteins of leptin receptor signalling. Therefore their down-regulation can be considered a useful approach to revert leptin resistance [39]. The inhibition of SOCS3 expression and/or activity could possibly lead to an interruption of the negative feedback loop related to leptin resistance and restore leptin activity. Accordingly, ObRb mutation in transgenic mice, disabling SOCS3 binding [40]. reduced food intake, increases leptin sensitivity and reduced weight gain. Besides SOCS3, also PTP1B inhibition seems to be an attractive target to overcome lentin resistance [41].

In fact deletion of PTP1B in mice increases lentin sensitivity, reduces body weight and increases energy expenditure. These animals also showed an improvement in glucose metabolism and uptake, and they were protected by DIO. The selective inhibition of PTP1B resulted in dampening of STAT3 activation by leptin in HEK cells. To date, inhibitors of PTP1B based on capability to bind PTPB1 active site (without hydrolysis) have been designed. In particular, thiazolidinedione compounds have been shown to exert anti obesity effects as PTP1B inhibitors and PPAR-a activators, ameliorating blood lipid profile in mice on high fat diet [42].

POMC neuron activation:- Last molecular targets of leptin effect on energy balance are POM neurons, therefore their activation seems another attractive strategy to overcome leptin receptor signal to induce a-MSH-mediated suppression of food intake and weight gain together with an increase in energy expenditure [43].

Increase in leptin receptor expression and cell surface localization:- An increase in ObR expression and its localization at the cell surface are key determinants for cell sensitivity to leptin [44]. We demonstrated that in leptin resistant ovariectomized obese rats, estradiol replacement therapy or long term raloxifene treatment, reduced leptin levels and body weight and restored leptin receptor expression both in adipose tissue and hypothalamus [45]. Unfortunately,

differently from rodent studies, a recent review of the literature regarding estrogen effect on leptin levels in post-menopausal women, did not show evident beneficial effects by hormonal intervention in modulating leptin levels and attenuating weight gain. Therefore, the authors discourage the hormonal intervention in relation to cardiovascular and neoplastic risk associated with the replacement therapy [46]. Previously, clinical studies showed an increase in leptin levels and body fat content in other studies reported an increase in leptin levels in treated woman, not related to change in fat mass. It has also been shown that metformin, acting at ObRb hypothalamic gene level, is able to increase receptor expression and leptin sensitivity, and exert an anorectic effect. Moreover, the inverse agonist of cannabinoid receptor 1, JD5037,can overcome leptin resistance and reduce weight gain [47].

Treatment Of Obesity Based On Leptin:-

Leptin analogous: Metreleptin is a once daily subcutaneously administered leptin analogue approved by the FDA in 2014 for use in people with leptin deficiency or congenital/acquired lipodystrophy, with good clinical results in these conditions. Whilst metreleptin monotherapy supports weight loss in obese individuals, it is not clinically meaningful with a mean 1.5 kg additional weight loss over 24 weeks noted in a previous trial [48]. To enhance the effect of leptin analogues, amylin mimetics such as pramlintide have been used in combination with metreleptin. One study found that use of the pramlintide/metreleptin combination resulted in 11.5 kg weight loss over 20 weeks compared with 7.4 kg and 7.9 kg weight loss respectively in participants receiving either metreleptin or pramlintide monotherapy. Unfortunately, the development of the combination therapy was discontinued in 2011 following commercial reassessment [49].

Phentermine and topiramate combination therapy: Phentermine plus topiramate food intake may be due to an increase in hypothalamic CRH, which is an anorexigenic neuropeptide [50]. Furthermore, TPM seems to reduce energy deposition even in the absence of changes in food intake, suggesting a role for TPM in increasing energy expenditure. Nonetheless, (TPM) in combination markedly decreased body weight in overweight and obese patients and the US. Food and Drug Administration just recommended this drug to be approved to treat obesity TPM treatment has been shown to reduce adiposity in humans and rodents. This reduction in adiposity is related to decreased food intake and reduced body fat gain. In rodents, the TPM treatment induced reduction in the molecular mechanisms by which TPM- induced weight loss occurs are contradictory and remain to be clarified [51].

CONCLUSION

Obesity is a global health concern till date, it having such strong epidemiological evidences which link it to various other health issues. Genetic factors like mutation in leptin signaling plays an important role in obesity. This influences both somatic and hereditary genomic events. Activation of specific pathways due to metabolic shift which is associated with obesity and tumor progression is contributed by these genetic factors along with the gut microbiome. Comprehensive approaches are required to examine leptin's role in obesity can be done by metagenomics, metatranscriptomics, metaproteomics and metabolomic studies. Further research should be targeted on the biology of the leptin focusing more on the acquired genetic variations and understand more about there interaction with the gut microbiome. Longitudinal studies focusing on unveiling these factors from early life to adulthood may contribute to future research in building critical preventive strategies, potentially leading to innovative treatments and managing obesity in a better way.

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