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Insights of Leptin as a Link to Congenital Leptin Deficiency and Exercise Effects

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Abstract:- Leptin, a white adipose secreted hormone, plays a central part within the control of nourishment admissions and vitality use, whereas Leptin mutation gene effects in congenital leptin deficiency (CLD), which leads to leptin deficiency. Therefore, there is a lack of circulating leptin, resulting in extreme obesity, severe overeating, and severe metabolic abnormalities. The physiological and pathophysiological parts of leptin in weight have been explored broadly since its revelation in 1994. However, the pathophysiological aspects of leptin or leptin receptor mutations as to how it causes hepatic steatosis and severe obesity has not been well explained. Hence, this submission aims to describe leptin and outline how it is associated with congenital leptin deficiency.

Keywords:- *Leptin, Congenital Leptin Deficiency, Lepbr, Obesity, Exercise and Leptin Mutation.*

I. INTRODUCTION

Leptin is a hormone that helps regulate metabolism. It diminishes nourishment admissions while increasing energy consumption, improving insulin sensitivity, and inhibiting liver fat production and fatty acid intake [8]. Therefore, patients with leptin deficiency due to leptin gene mutation or circulating leptin deficiency (such as CLD) show severe hyperphagocytosis, insulin resistance, and hepatic steatosis [9]. Leptin is a kind of adipocyte hormone, which is mainly produced in adipose tissue. Its circulating level in balanced homeostasis is closely related to body fat. It plays an important role in regulating energy balance, neuroendocrine-immune function, glucose, lipid, and bone metabolism [10, 11]. The leptin receptor is found throughout the body, including the central nervous system, and regulates neuroendocrine function, eating behaviour, and energy intake [11]. It is known for crossing the blood-brain boundary, which controls vitality basically through the arcuate core of hypothalamus homeostasis.

The foremost well-known work of leptin is to direct body weight and vitality adjustment. Therefore, without leptin, the homeostasis of the human body will change seriously. CLD is one of the potentially fatal changes observed due to leptin gene mutation. In addition, patients with CLD have been reported to have morbid obesity, decreased cognitive development, and potentially deadly T cell hyporesponsiveness.

In addition, studies in humans have shown that the ability of peripheral leptin to enter the brain is significantly reduced. In a study, the peripheral and central leptin levels of obese and lean people were measured. The results showed that the peripheral leptin level of obese people was significantly higher than that of lean people. This analysis showed that in obese individuals, the proportion was 3-4 times less than that in lean individuals [12]. This result further shows that the ability of leptin to transport from blood to brain in obese people is reduced, so there is a situation leading to hyperphagia. However, the absolute concentration of leptin in the blood of obese people is higher than that of lean people [13]. The findings of a study by Johnston JM et al.[14] indicating peripheral injection of exogenous leptin over physiological concentration did not activate the leptin signaling pathway in the central nervous system of DIO mice were further highlighted.

II. LEPTIN SIGNALING

LbRb has 3 tyrosine residues in its cytoplasmic sol domain. When leptin binds to LbRb, Janus kinase (Jak) is cross-phosphorylated, resulting in phosphorylation of tyrosine residues in the activated cytoplasmic sol domain. Three major intracellular signaling pathways occur in LbRb. Phosphorylation of tyrosine residue 1138 helps activate the signaling and transcriptional activator (STAT) families [15]. It has been demonstrated that leptin selects STAT1, STAT3, STAT5, and STAT6 in vitro but selects the only STAT3 in vivo. After dimerization, the STAT moves to the nucleus and causes expression of the suppressor of cytokine signaling3 (SOCS3), which then inhibits proximal leptin signaling [16]. The second pathway involves SH2 containing phosphatase2 (SHP2) and extracellular signal-regulated kinase (ERK). Phosphorylation of tyrosine buildup 985 can enlist SHP2 at that point enroll growth factor receptor binding 2 (Grb2). This may actuate the ERK pathway through Ras, eventually actuating cfos expression. Jak2 can too intervene Grb2RasERK pathway and affront receptor substrate (IRS) freely of tyrosine phosphorylation locales on LbRb [15, 16].

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III. LEPTIN MECHANISM

Leptin (16 kD protein, encoding 167 amino acids) is mainly secreted by white adipose tissue. Its processing involves the cleavage of 21 amino acids N-terminal signal sequence, resulting in the mature functional non-glycosylated protein of 146 amino acids [17] Leptin modulates energy intake and expenditure by working on the arcuate nucleus of the hypothalamus [18]. It acts by binding to specific leptin receptors (LEPR) throughout the central nervous system (CNS). The extracellular ligand-binding, transmembrane, and cytoplasmic signal transduction domains of LEPR belong to the interleukin-6 family of class I cytokine receptors [19]. Six LEPR subtypes labeled "lepra-f" result from alternative splicing, which can be classified as secretory (Lepre), short (lepra, leprc, leprd, and leprf), or long (lepra, leprc, leprd, and leprf) (leprb).

LbRa and LbRc mainly exist in the choroid plexus and cerebral microvascular system [20], indicating that they play a role in the blood-brain barrier transport. LbRb comprises 1,162 amino acids, representing the longest intracellular domain (about 306 amino acids), and is highly expressed in the hypothalamus, heart, liver, and lung. Neuron-specific ablation of LbRb leads to obesity, suggesting that the central nervous system (CNS) plays a role in the energy expenditure effects of leptin [16]. LbRe lacks the intracellular transmembrane domain and is a soluble LR (sLBR) [15]. During circulation, leptin can be in free form or combined with soluble LR. LbRe may be involved in regulating the circulating levels of leptin, transport [16, 21], and the biological activity of leptin [22]. Initially, the direct effects of leptin were thought to be limited to the central nervous system. However, the general distribution of LR in non-neural tissues implies the diversity of the probability of biological effects associated with leptin [23].

IV. CONGENITAL LEPTIN DEFICIENCY

Leptin mutation is the most common cause of congenital leptin deficiency, which leads to obesity and hypothalamic axis imbalance [26, 27]. It's a hereditary genetic disorder linked to extreme obesity at a young age. These mutations in the leptin (LEP) gene cause nonsense-mediated mRNA degradation, secretion abnormalities, or physiologically inert leptin to be produced. As a result, there is a lack of circulating leptin, resulting in extreme obesity, severe overeating, and severe metabolic abnormalities due to a rare single gene mutation [28]. In addition, congenital leptin deficiency (LEPR) has proven to destroy leptin signal transduction in mice and humans, resulting in severe obesity, binging, various biochemical changes, and stalled puberty due to gonadotropin dysfunction [29]

V. LEPTIN MUTATION

The Leptin Mutation gene results in congenital leptin deficiency, which leads to leptin deficiency. As a result, the pathways that cause satiety are disrupted, resulting in increased hunger and, to fulfill desire, weight gain. Different mutations have been reported in leptin patients, one of which is a guanine deletion in the gene. This is the first evidence for subjects with congenital leptin deficiency that LEP is involved in regulating energy biochemistry gene 123 [30]. Eleven mutations in LEP were identified, including p.l72s, p.n103k, p.r105w, p.h118l, p.S141C, p.w121x, c.104j 106deltca, c.135del3bp, c.398delg, c.481482help and c.163c [t]. The incidence of some of these mutations was given in [31-33]. Many studies have shown that leptin is related to energy consumption, so mutations in leptin can affect the body's metabolism, leading to weight gain and severe obesity.

Furthermore, two unique frameshift mutations in p.c186afsx27 and p.h160lfsx9 shortened the LEPR protein, leaving it without the leptin binding (CRH2) domain is required for all LEPR subtypes' leptin signal transduction. In addition, both mutations impair the extracellular N-terminal of the LEPR protein, causing congenital leptin insufficiency in all subtypes. The extremely damaging character of these frameshift mutations is likewise consistent with patients' fast weight gain and excessive obesity [29].

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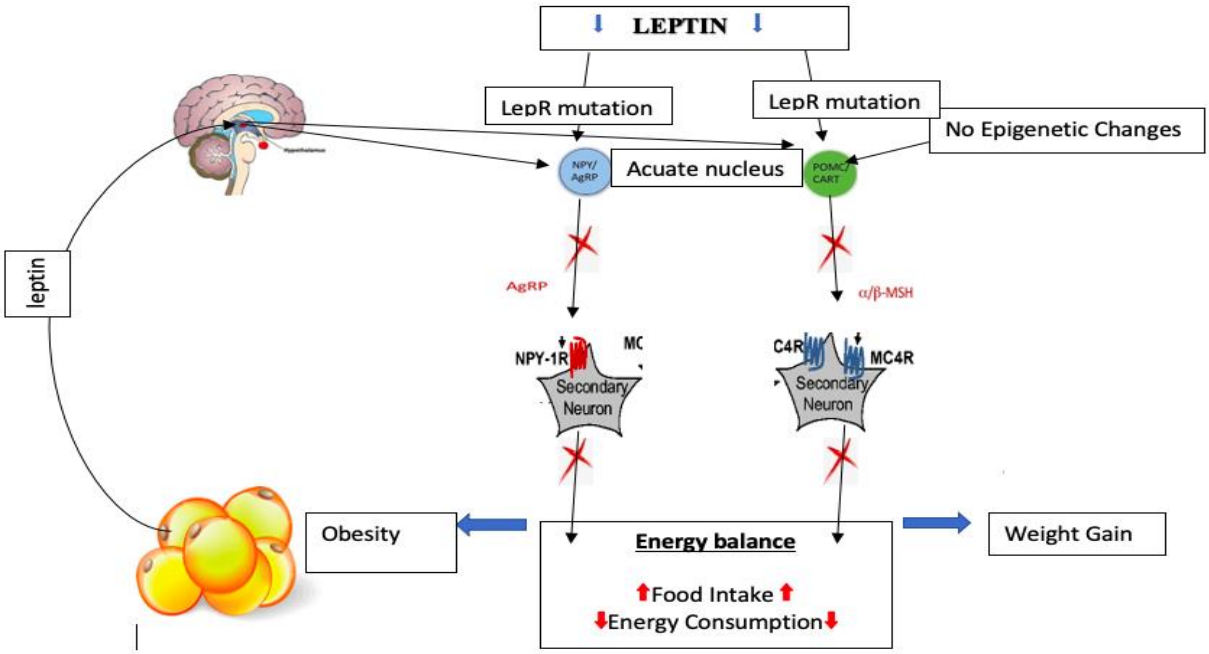

Fig 1: First, fat cells secrete leptin. Leptin then is supposed to bind to the leptin receptor (LepR) however due to lepR mutation, binding is inhibited, thus the opioid promelanocortin (POMC) can not expresses αMSH-releasing neuron, therefore, αMSH can not activate MC4R in the paraventricular hypothalamic nucleus (PVN), inactivated MC4R can not transmits a satiety signal to the brain and body to stop eating which leads to overeating. Another way that leptin is supposed to control energy intake it should be by expressing the AgRP / Neuropeptide Y (NPY) appetite of neurons. However, when leptin tries to stimulate mutated LepR in AgRP / NPY neurons, leads to expression of AgRP being inactivated. The combination of MC4R and AgRP increases appetite and food intake [39].

In a study by Sadia s et al., 62 seriously corpulent Pakistani kids, 17 conveyed LEP mutations, and 3 conveyed MC4R homozygous transformations [34]. Interestingly, MC4R heterozygous carriers are not obese, suggesting that the penetrance of the disease is lower in rural Pakistan than in western countries. In another study conducted by the same team, they identified two new pathogenic leptin mutations in the homozygous state from the same cohort. They found homozygous leptin mutations in the subjects, which involved base substitution at the intron/exon junction at the splice site of exon 15. This substitution is predicted to result in aberrant splicing of leptin transcripts due to the skipping of exon 15. Therefore, the mutant gene will only encode the first 798 amino acids in the extracellular domain of leprosy.

Homozygous leprosy mutations at the splice donor site of exon 16 were also reported in three siblings of a close relative family [35]. The results showed that exon 16 was skipped during transcription, resulting in an 831 amino acid protein encoding the extracellular domain of LEPR, similar to the short soluble subtype of the leptin receptor. It was further proved that the protein was secreted in the blood and combined with circulating leptin, resulting in high levels of binding hormone and total hormone [35]. The second deletion of leptin mutation leads to premature codon termination, translating into a truncated leptin protein containing the first 558 amino acid extracellular domain and lacking transmembrane and intracellular domain receptors. The leptin level in peripheral blood of homozygous leprosy gene mutation was increased. Still, it was similar to that of age-matched subjects with wild-type leprosy gene sequence in the same cohort. Both subjects showed extreme obesity and gluttony. Their data are also consistent with animal studies, in which leptin-deficient mice had the same phenotype [34]. However, research has proven that leptin supplementation may change the brain circuits involved in food reward perception in the case of leptin insufficiency, resulting in weight loss.

Leptin use also altered the response of these patients to visual food cues on fMRI. In a patient with congenital leptin deficiency, 3-day and 6-month leptin replacement led to changes in reward-related activities for food cues [14, 36]. One week of leptin supplementation reduced the activation of food pictures in the striatum in another investigation of two patients with the same condition [37]. In addition, leptin substitution decreased food image activity in attention/satiety-related areas while increasing cognitive control and satiety-related areas in the other three individuals [38].

VI. EFFECT OF EXERCISE ON LEPTIN LEVELS AND LEPTIN RESISTANCE

Leptin has been proven to create a negative energy balance by anorectic and thermogenic actions since its discovery in 1994[9]. [40, 41]. Leptin levels were also observed to be lower in exercise-trained people [40] who followed exercise programs [42]. This is in line with the findings of Pasman et al. [43] who found a significant link between the number of hours of exercise and plasma leptin

after a 16-month diet and exercise training program [43]. Leptin levels have been reported to rise with age, along with leptin resistance. Rostas and colleagues discovered that exercise training promotes lower leptin concentrations in middle-aged and older overweight and obese people, with strength training producing a greater leptin reduction than aerobic training alone. This implies that exercise modality has an effect on plasma leptin, which could be due to the fact that resistance and aerobic exercise produce different stimuli [44]. A meta-analysis found that a training intervention lowers leptin levels in middle-aged and elderly obese people.[44]

VII. EFFECTS OF LEPTIN MUTATION ON OTHER SYSTEMS

The hypothalamic arcuate nucleus' agouti-related peptide and pro-opiomelanocortin neurons mediate leptin's effects on innervation. In both populations, deletion of the gene encoding the leptin receptor results in diminished fat innervation. These agouti-related peptide and pro-opiomelanocortin neurons in the hypothalamus's paraventricular nucleus act through brain-derived neurotropic factor-expressing neurons (BDNFPVH). BDNFPVH deletion reduces the effects of leptin on innervation. These findings reveal that leptin signaling governs sympathetic architectural plasticity in adipose tissue via a top-down neuronal pathway that is important for energy homeostasis.[45]

In addition, the more severe the abnormalities of individuals with low leptin levels the more it affects other body homeostasis such as blood pressure, heart rate, insulin levels as well as affecting body development. This raises the prospect that leptin could be used to treat other diseases that arise as a result of leptin deficiency. For example, despite bone age indicating that one should have entered puberty in adolescent, one female patient with leptin insufficiency did not, however leptin treatment resulted in the onset of menses. This means that leptin could be employed to treat delayed puberty[46].

Leptin has too surfaced as a potential cause of the irregular cardiovascular work in corpulence, free of its known impacts on nourishment admissions and vitality cons umption[47, 48]. Central weight is considered the foundation for the onset of metabolic disorder or cardiometabolic disorder, a cluster of obliterating metabolic disarranges including insulin resist ance, hypertension, weight, and high low-density lipoprotein cholesterol and triglyceride levels [49, 50] In a review done by Jun R [51] about impaired cardiac function in Leptin-Deficient Mice reported that the cessation of leptin signalling in both leptin deficiency (ob/ob) and leptin receptor deficiency (db/db) is likely to be reversed by leptin administration in leptin deficiency following age-related ventricular hypertrophy independent of obesity [52]. Cardiac hypertrophy is the heart's compensatory mechanism in response to health conditions in the heart, such as myocardial infarction or heart failure. Both leptin-deficient (ob/ob) and LR-deficient (db/db) mice show apparent CAR diacromial hypertrophy, decreased systolic, decreased survival [53], demonstrating the role of leptin in the structure and shape of the heart. Weight, a basic arbiter of ventricular hypertrophy, can result from either a lack of leptin or receptor insensitivity [30]. In spite of the fact that leptin insufficiency or disturbed leptin signaling is known to trigger cardiac dysfunction [48, 54, 55], clinical reality must be considered since most obese people show elevated plasma leptin levels.

Besides, alter in plasma leptin levels, and leptin signaling incorporates a significant neurotic affect on body weight control. Both leptin insufficiency and leptin receptor imperfection are adequate to deliver obesity of genetic origin [56]. Be that as it may, the foremost common trigger of corpulence isn't hereditary absconds of leptin or its receptor but or maybe depends on indulging or high-fat diet, which may quickly increment plasma leptin levels [57, 58]

VIII. CONCLUSION

The importance of leptin in the energy balance is most obvious in leptin deficiency. Therefore, total leptin deficiency in patients with congenital leptin deficiency leads to overeating severe obesity insulin resistance, diabetes, steatosis, and other metabolic syndrome characteristics. However, leptin treatment reversed these characteristics, resulting in significant reductions in energy intake, energy expenditure, body weight, and fat. A study in female ob/ob mice showed that mice treated with leptin replacement lost 17% of their body weight, significantly reduced food intake, and showed a rapid decline in blood glucose levels. LDLR protein decreased by 63%. In their cohort, only women, including patients with multiple forms of lipodystrophy (congenital systemic lipodystrophy), were included. Leptin treatment lowered BMI, fasting plasma insulin level, and hemoglobin A1c levels considerably. Leptin can reduce triglycerides, total cholesterol, and low-density lipoprotein cholesterol by 20% to 40%, according to prior studies [59].

AUTHOR CONTRIBUTIONS

KKK conceived the original copy and composed the primary draft. RW and ACPM revised the drafts. All authors contributed to the article and affirmed the submission of this version.

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