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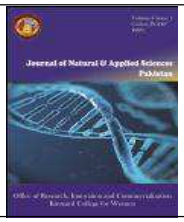

ASSOCIATION OF LEPTIN HORMONE WITH OBESITY

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Abstract

A proper coordination among the different body parts is crucial for any living organism, especially for the more complex living beings that is a human. This coordination is achieved through an interconnected network of various systems such as the circulatory system, cardiovascular system, digestive system and so forth. Nervous system and endocrine system are the major coordinating systems in a human body. Endocrine system regulates various other systems through hormonal secretions that target specific tissues. Leptin is one of these hormones which has been observed to be associated with food digestion and influence weight gain or obesity. Normally, this hormone is known to be an anti-obesity hormone as it targets the hypothalamus and decrease appetite. While obesity is caused when a mutated form of leptin ob gene is present, causing lower expression that results into abnormally high appetite. The present study aims to assess the influence of leptin ob gene on various other systems of the body that ultimately lead to obesity. It also aims to find potential solutions to the resulting irregularities. This study is a research based on thorough survey of 121 research articles. It has been found that Leptin ob gene, in addition to causing obesity, is related to misfunctioning and disorders of various other systems such as the central nervous system and the immune system. Leptin replacement therapies have been found useful in this regard to treat obese cases through proper regulation of immune system and hormonal responses. While in some other cases, where a diet induced obesity leads to leptin resistance that is, even if the hormone is present is correct amount in the body, it is ineffective and leads to abnormally high levels of leptin in the body, leptin may lead to insulin resistance and thus become a possible leading cause for diabetes. Such kind of leptin resistance can be reversed through sufficient changes in the diet and physical activities. It is important to look into the detailed pathophysiology of leptin resistance which as of yet is unclear. Therefore, more research is required to understand the working of leptin ob gene and its relationship with health defects and also to discover the most effective approach for reversing these defects.

1. Introduction

Human body is complex based upon the interrelated working of differed systems such as digestive system, respiratory system, circulatory system, endocrine system, nervous system and so on. The endocrine system is one of the most important systems of the body that regulates all other systems. It is also known as 'Chemical Messenger System', having glands which release different hormones that bind to specific targets and generate a response (Marieb & Elaine, 2014). Hormones are chemical molecules which are important for the physiology and behavior of different body parts by controlling various mechanisms, for example, respiration, tissue function, sleep, excretion, stress, growth, and development. They show signal transduction mechanisms in which a specific protein binds to a specific target and activate the cell for a response. Some hormones are peptide and amine in nature and many are water-soluble in nature, for example, steroid hormones (N, 2008).

In the endocrine system, a complex relation of glands, hormones, and target. Hormones directly communicate with the nervous system. This system is also present in animals and plants and control physiological activities for example growth, sugar levels and puberty (Ruhs, Nolze & Grossmann, 2014, p. 107). For food intake and digestion, endocrine hormones play an important role. Due to hormonal regulations and physical activities, energy is produced which helps to digest the food. In the present age, the physical activity of many peoples has been decreased which leads to different diseases e.g. obesity and cardiovascular diseases. Through food intake, we obtain energy which helps us perform our daily tasks. There are different homeostatic regulators which are present in our body for controlling energy transformations (Coll AP, Farooqi IS & O'Rahilly S, 2007, p. 107).

Food digestion is a process that starts in the mouth when food is chewed and mixed with saliva that contains amylase enzyme to break down starch into small particles (maltose and carbohydrates) (Lundbery J, 2005, p. 1). After passing from esophagus, food reaches into the stomach where two hormones i.e. Secretin and Cholecystokinin (CCK) have significant importance for protein digestion. G cells release gastric juice which contains bicarbonates, ions, and enzymes that help in the digestion of food. Secretin hormone is released to inhibit the secretions of gastric juice, followed by the release of CCK from the pancreas that enhances the enzymatic secretions (Ivy AC & Gray JS, 2011, p. 236). The pancreatic juice helps in the digestion of peptides present in food followed by the digestion of food (Polak JM & Bloom SR, 2001, p. 8).

Increased food intake together with improper digestion leads to obesity which is commonly observed among increasing number of individuals belonging to both the developed and under-developed countries (Reis AF & Velho G, 2011, p. 319). Obesity is mainly caused by high-calorie food intake, sweetened beverages, vegetable oils and high energy carbohydrate chunks but the major cause of obesity is a lack of physical activity. In almost every developed country, around 22% of the adults fall into the obese category and the major reason for this is the huge consumption of fast foods (Darvall KA, Bradbury AW & Adam DJ, 2005, p. 224). Obesity causes increase in the adipose tissue in body which is considered as a major cause of several other diseases such as diabetes, cardiovascular disease, cancer and hypertension (Sarnali T & PK M, 2011, p. 235). Increase in the rate of obesity may also lead to different psychiatric disorders as observed in a number of people. A study has been conducted on 249 patients which showed that 18% suffered from obsessive-compulsive disorder, 30% from phobia and somatization while 13.6% people had different sociological disorders (Rosik CH, 2005, p. 676).

In other studies, obesity was observed to be associated with leptin which is secreted from adipose tissue and acts on the brain for inhibiting the intake of food (Zhang Y, Proenca Friedman JM., 1998, p. 250). This role of leptin towards decreasing hunger and appetite is the main reason for its use in the treatment of obesity as leptin injections are administered to the obese patients (Zhang Y, Proenca R & Friedman JM., 2011, p. 1408). Based upon different studies, it has been proved that leptin is an anti-obesity hormone which is transported to the brain where in binds to the leptin receptors present in the hypothalamus due to which JAK-STAT 3

activates and cause conquest of orexigenic peptides and increase anorexigenic peptides which suppresses food intake (Welt CK & Mantzoros CS, 2003, p. 289). However, SOCS3 acts as an inhibitor and flows in the bloodstream to inhibit overexpression of leptin (Oral EA, Simha V, Ruiz E & Gorden P. ,2002, p. 1569).

Low levels of leptin and mutations in the leptin ob gene may also cause obesity in humans. However, leptin replacement therapies can cause alterations in immunity levels, hormones, and hypothalamus neuropeptides to correct leptin functioning (Farooqi IS, Keogh JM & O'rahilly S., 2001, p. 988). This therapy is critically important for maintaining normal metabolic processing of

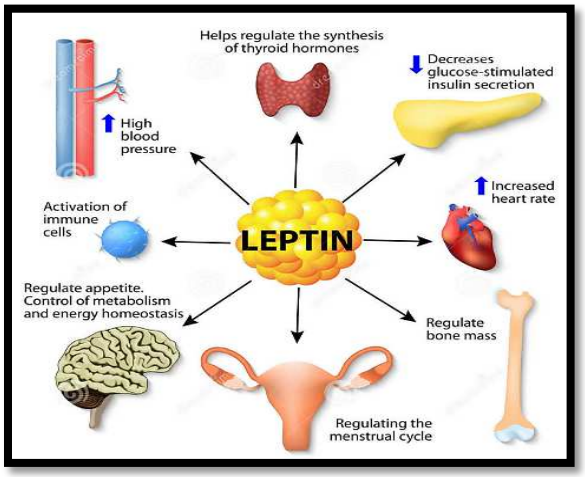

Figure 1: Role of leptin hormone in body.

(Retrieved from: https://healthjade.com/what-is-the-hormone-leptin-and-how-does-it-relate-to-my-weight/)

According to different researches defects or mutations in the leptin gene also causes severe obesity (Houseknecht KL & Spurlock ME, 1998, p. 1406). Leptin gene codes for 167 amino acids and is important for the regulation of adipose tissue mass and suppression of food intake (Clement K, 1999, p. 52). It plays an important role in male and female reproductive organs, kidney and lung development. Polymorphisms in the three genes of leptin e.g. LEP, receptor gene (LEPR) and peroxisome proliferator-activated receptor-gamma gene (PPARG), leads to obesity (Rosmond R., 2008, p. 1141). All of these genetic mutations are present at different sites due to which complete the body's digestive system and related areas where leptin plays an important role. In some studies, it has been stated that the reduced levels of leptin would cause weight loss and effect energy expenditure which in turn promote weight gain (Fried SK, & Laferrère B., 2000, p. 1410). Due to leptin therapies, the effect of diet and drug treatments would sustain in the treatment of obese patients (Wasim M., 2015, p. 34). Besides obesity and hunger control, leptin plays an important role in other parts of the body e.g. regulation of menstrual cycle, heart rate, and bone mass (Baratta M., 2002, p. 224). However, it has the most important role in obesity control which makes it suitable to treat obese cases as during the leptin replacement therapy (Martin LJ, Mahaney MC & Comuzzie AG. 2002, p. 283).

sequence of the gene is altered and causes obesity in an individual (Chagnon YC & Bouchard C., 2003, p. 314).

Obesity is considered as a major public health concern, all around the world, as it leads to many other chronic diseases (Paracchini V & Taioli E, 2015, p. 328). Some researchers believe that genetic variations in the leptin are solely responsible for causing obesity but there is still a doubt as many other researchers consider that obesity is caused by both the gene and environmental interactions (Ahima RS & Flier JS. 2000, p. 1). Different researches have been conducted to study the gene-gene interaction and gene-environment interactions, also involving the meta-analysis (Pond C, 2001, p. 579). However, based on the current data, it is evident that an association certainly lies between the leptin gene and its hormonal levels that critically regulate food digestion together with the environmental factors which are also very crucial for determining the risk of obesity among mutated leptin gene individuals (D.L. Coleman, 2003, p. 67).

This study is based on an evaluation of 121 research articles and aims to assess the possible causes of obesity, as it specifically related to the mutated ob gene and hormonal imbalance of leptin in the body (Kennedy GC, 1953, p. 34). It also aims to identify the disorders of other body systems such as nervous system and the immune system, owing to leptin imbalance and also suggests some potential treatments available for these disorders and leptin associated obesity (M.X. Zarrow & J.L. McCarthy. 1964, p. 295).

All vertebrates and mammals have the capability to survive in a disparaging condition where food is not enough to support life (J.C. Finerty, 1994, p. 34). The mammals and vertebrates have adipose tissue where lipids (Triglycerides TAG: hydrophobic in nature, store in large quantity, and have more energy per unit as compared to other nutrients) are stored and produce fatty acids by the process lipogenesis (enzymatic reactions) (D.L. Coleman, 1973, p. 295) that helps them to survive in disparaging condition. On the other hand, the adipose tissue not only serves as energy reservoir (white adipocyte tissue: present in adults) and insulator (brown adipocyte tissue presents in infants) but also has the capacity to produce hormone and is therefore, attributed to have an endocrinal role. Hormone produced by the adipocyte cells of the adipose tissue is known as 'adipokines'. Due to its dynamic function, it is also involved in metabolic regulation through the secretion of the hormone leptin. (K.P. Hummel & D. L. Coleman, 1966, p. 1128).

In 1949, at Jackson laboratories, in Bar Harbor, a research was conducted to observe obesity in the mouse. This obese mouse was different from its wild littermates because it had weight four times more as compared to other littermates at the age of 4 to 6 weeks. No effect in lifespan was observed for 12 months age (Y. Zhang & J.M. Friedman, 1994, p. 429). Obese animals were sterile and they were the result of heterozygous mating, having the characteristic of the recessive gene as 3:1, and the designated gene was the ob gene. ob/ob obese mouse came from noninbred stock which was considered as diabetes model because of massive obesity and hyperglycemia (G. R. Hervey, 1969, p. 630). Autosomal recessive gene present on the chromosome 6 resulted from inherited syndrome. The mutation was seen to transfer to the inbred strain (C57BL/6J) by a number of intercross mating. By this cross-intercross mating resultant (BL/6) obese mouse had obesity, hyperglycemia, elevated plasma, hyperphagia and 10 to 50 time more insulin concentration that resulted into increased size and number of beta-cells of the pancreas. These mutants were also infertile (both sexes) (D.L. Coleman, 1973, p. 163).

Gordon Kennedy, in 1953, proposed a lipostatic theory in which he stated that fat mass works as the set point of energy balance, such as the stored fat sends feedback to the hypothalamus (the region of brain controller of feeding behavior) which signals signals for energy requirement (D.L. Coleman, and K.P. Hummel, 1973, p. 57). He also suggested that these feedback factors are the circulating metabolites. To check the autosomal recessive gene mutation, parabiosis was performed which involves the union of two organisms surgically i.e. conjoined twins (D.L. Coleman, 1972, p. 399). Endocrinal substance was shown to be involved in the activation of adiposity and satiety (M. A. Pel ley mounter & T. Boone, 1998, p. 828). Further studies support the fact that satiety center present in the hypothalamus and hypothalamic lesion result in obesity. Normal and obese mouse was paraboised giving a shocking result of severe weight loss and appetite in the normal mouse due to an excess amount of adipose tissue in hypothalamic lession that resulted in higher production of leptin (Clement, K., Vaisse, C. & Guy-Grand, B, 1998, p. 633).

In 1966, db/db diabetic mouse strain was observed at Jackson laboratory in Doug Coleman where the mutation (metabolic disturbance resembling diabetes mellitus) in the inbred strain (C57BL/KS) was studied (Fruhbeck G & Burrel MA, 2001, p. 492). Similar in appearance to the mutant mouse (phenotypically) but had shortened lifespan. These were also observed to show 200mg/dl blood sugar concentration by 8 weeks of age and 300mg/dl by 10 weeks of age and the inheritance of autosomal recessive gene. Diabetic homozygotes were obese, non-fertile and hyperglycemic, however, heterozygous could not be distinguished from normal mouse visually. db mutation is located on chromosome 4 (Lee GH & Lee JI, 1996, p. 96). At first, food restriction was used to control weight and was shown to be successful with obese ob/ob mouse but failed in case of db/db diabetic mouse which could not survive with low food intake (Chen H & Ellis SJ, 1996, p. 552).

Coleman and his co-workers used the paraboitic method to describe the nature of obese ob/ob mouse in his institution (Mueller

WM & Warden CH, 1998, p. 2367). He paraboised the normal and ob/ob mouse that resulted into the ob/ob genotype of mouse, showing reduced/slower weight gain and reached normal body weight. Moreover, the deficiency of satiety factor in ob/ob mouse does not affect the normal mouse. Plasma insulin and blood glucose level were also improved in the ob/ob mouse. When they paraboised db/db mouse with a normal mouse, rapid loss of weight in normal mouse was observed but they died after 50 days of surgery by apparent starvation (Vaisse C & Friedman JM, 1997, p. 73). Through this experimentation, it was proved that ob gene present in normal mouse could help reduce obesity in ob/ob mouse, but in db/db mouse the mutation resulted into loss in ob gene receptor and these mouse were made resistant to the product of ob gene. This mutant breed produced an excess amount of ob gene product because of the increased amount of adipose tissue and suppressed appetite in normal mouse (Leroy P & Ailhaud G, 1996, p. 132).

In 1994, Jeffery Friedman and his colleagues at the Rockfeller University, Howard Hughes Medical Institute, continued the research to identify satiety signal (Kristensen, P. & Hastrup, 1998, p. 156). They used molecular biology techniques to find obesity hormone. They successfully cloned and sequenced mouse ob gene and its human homologue. They described that ob gene of adipose tissue encodes 4.5 kb mRNA having 167 amino acids, 16 kDa in weight, with three exons, two introns and is located on chromosome 7 on the long arm q at position 32.1. Mice and human have 84% amino acid homology (Huszar, D. & Lee, F, 1997, p. 984). Leptin is a Geek word derived from 'Leptos', meaning lean. As leptin is an endocrinal hormone, it is present in the body in protein bounded and free-state and found in the blood circulation after secretion from the adipose tissue (Krude, H. & Gruters, A, 1998).

On the locus of db/db mouse gene, encoding the leptin family, alternative splicing occurs. Leptin receptors belong to class I cytokine receptor family which includes growth hormone (GH), erythropoietin, several interleukins (IL-2, IL-7) and prolactin (Balthasar, N., Coppari & Lowell, B. B, 2004). By alternative splicing, OB Receptor b (OB-Rb) (Guo, L & Bjorbaek, C, 2004) is produced in spliced form which has functional role in the hypothalamus and has a large intracellular domain (Bates, S. H. & Myers, 2003). OB-Rb is strongly expressed in the hypothalamus among all the six spliced forms (Cui, Y. & F., Yang, 2004).

Signal transduction pathway was also mediated by the attachment of leptin on the leptin receptor (OB-Rb) and activation of the signaling molecules, Janus Kinase (JAK2) (Gao, Q., Morino, K. & Fu, X. Y, 2004). The JAK2 begins phosphorylation of multiple tyrosine residues (Tyr1138) in the cytoplasmic domain of the leptin receptor (OB-Rb), followed by Signal Transducing and Activation of Transcription (STAT3) that binds with Tyr1138, phosphorylating the STAT3 (Banks, A. S., Davis, S & Myers, M. G, 2000). This phosphorylation, dimerization and translocation to the nucleus modulates the transcriptional activity of many target genes (Bjorbaek, C. & Flier, J. S. 2011, p. 30060). Energy balance is regulated through the transcriptional regulation of various neuropeptides involved in the feeding signaling process (Bjorbaek, C., Elmquist, J. K. & Flier, J. S, (1998). Expression was increased in case of anorectic neuropeptides such as propiomelanocortin (POMC), cocaine and amphetamine-regulated transcript (CART) and orexigenic neuropeptides such as neuropeptide Y (NPY), Agouti-related peptide (AgRP) and melanin-concentrating hormone (MCH) (Donald F & Behan SHC, 2012). POMC upregulation requires STAT3 binding with its promoter region and Tyr1138 phosphorylation. α-Melanocyte (Chadwick JMW, 2014) stimulating hormone (αMSH) it to be activated by POMC which is the melanocyte 4 receptor (MC4R) agonist while AgRP is the antagonist of MC4R which is down-regulated by leptin binding. Severe obesity in human and rodents occurs through the mutation in POMC and MC4R gene (Reaven GM, 2014, p. 159). OB-Rb activation prompts the mRNA in the hypothalmic where specific supressors (SOCS3) rectly bind to STAT to generate response (DeFronzo RA & Ferrannini E, 1991). SOSC3 exists in SH2 domain, containg a protein that can bind with

the phosphorylated Tyr985 and inhibit the JAK2 activity while blocking leptin receptor signaling mechanism (Flegal KM & Ogden C, 2002, 760).

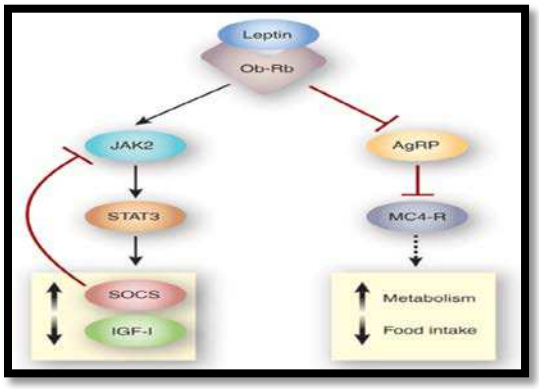

Figure 2: Leptin signal transduction mechanism.

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2. Causes of Obesity

According to WHO, obesity is an abnormal accumulation of fats in the body (Qianghua Xia1 & Struan FA Grant, 2013). It was first recognized as a disease by the ancient Hippocrates, a Greek physician, when he noted sudden death to be more common in obese people than in lean people (Hebebrand J, 2003). Insulin resistance generally leads to obesity (Bell CG & Froguel P, 2005, p. 234) which ultimately leads to a number of negative effects like, hypertension, stroke, cardiovascular diseases and other physical disabilities like joint pains etc. (Scherag A, 2010). It is a common perception that obesity is the leading cause of adverse health outcomes. In the 1970s, a children population survey for obesity was conducted where BMI were recorded in order to evaluate the possible health concerns (Speliotes EK, 2010). Obesity can be an after effect of many kind of acts and conditions. Genetics is one of the major causes of human obesity (Walley AJ & Froguel P, 2003). The evidence for the involvement of genetics for obesity can be stated by the experiment of twin studies. Since, monozygotic twins share more genetic similarity than dizygotic twins. So fat mass co-ordinance for MZ twins was more as compared to DZ twins (Boutin P, 2003, p. 68). In 2010, GWAS of childhood obesity was published which stated two loci for the obesity by French and German groups (Tanyolac S, 2009). These loci were *TNKS/MSRA* and *SDCCAG8* (Meyre D, 2005, p. 870). According to one study, the trait loci for body weight and height was found to be ecto-nucleotide pyrophosphatase (ENPP1), glutamic acid decarboxylase (GAD2) and solute carrier family 6 and member 14 (SLC6A14) (Durand E, 2004, p. 2484). Development of insulin resistance is also a major cause of obesity (Reaven GM. Banting lecture, 1988). Variants by which the leptin gene along with its receptor is encoded are linked to obesity and increased Body Mass Index (Mizuta E, 2008). Adinopectin is hormone that has reduced levels in obesity and type 2 diabetes (Diez JJ & Iglesias P, 2003). It is involved in the regulation of glucose fatty acids (Ukkola O & Santaniemi M, 2002). Over eating, lazy lifestyle and certain medications like antidepressants gradually leads to weight gain (Ness-Abramof R1 & Apovian CM, 2005). Therapies of psychotropic have a common side-effect of weight gain. Anti-depressants like amitriptyline, serotonin reuptake inhibitors and mirtazapine influences gain of weight (Australian Bureau of Statistics, 2011). Mood stabilizers also take part in the gaining of weight. Gain of weight as a side-effect of medications is majorly due to the disturbance in hormonal level, lipid profile and blood pressure (Myers MG & Leshan RL, 2009). The amount of energy intake and the amount of energy expenditure, if is disturbed, leads to obesity. The amount of energy requirement by the human body varies from person to person mainly depending on the type of lifestyle, size of body, age and other activities (Rosenbaum M, Leibel RL., 1999, p. 914). Energy expenditure occurs by the metabolism to maintain vital body processes, usage of energy during digestion and by the movement of muscles (Ahima RS & Elmquist JK., 2000). Increase in leptin levels also cause obesity. Leptin hormone is released by the fat cells (Halaas JL, Gajiwala KS & Friedman JM., 1996). In the brain, when this hormone is attached to LEPR-B (leptin's receptor), food

intake is reduced but the expenditure of energy increases. According to experimental data, leptin is involved in the defense system against the depletion of body fat. In this way, it helps in the maintenance and fitness of reproduction and survival of an organism (Chehab FF & Lim ME, Lu R., 1996). Decrease in leptin causes weight loss and loss of normal energy balance. If resistance to leptin occurs due to prolonged increased BMI, obesity occurs along with insulin resistance (Farooqi IS, Jebb SA & O'Rahilly S., 2008).

3. Relation of leptin with obesity

The main role of leptin is to maintain and conserve energy in the body (Frederich RC & Flier JS., 1995). The amount of plasma leptin concentration is directly proportional to the amount of fat in the body (Schwartz MW., 2000). The ups and downs of leptin are regulated by various hormones in the body. The up-regulation of leptin is done by insulin and down-regulation by catecholamines. Tumor necrosis factor-α also increases the secretion of leptin (Montague CT., 1997, p. 904). Triglycerides accumulate in the adipocytes due to which they increase in size and in turn synthesize more leptin. The main control center is hypothalamus (Fredrick SK., 2000, p. 1407).

Adipocytes are the fat cells that secrete leptin (Hafizuallah A. M., 2005, p. 250). Resistance to leptin or its complete deficiency causes life-threatening obesity. With the increase in leptin levels, the adiposity also increases and it induces negative feedback to the center of the brain that is involved in controlling the energy homeostasis (Zhang Y., 1994, p. 1569). Leptin deficiency is not associated with obesity, instead, the high levels of leptin lead to obesity (Ahima R.S., 1996, p. 250).

In the case of fasting or weight loss the leptin levels fall down and it leads to changes in hormone levels and energy levels (Flier J.S., 1998). When there are low leptin levels it signals for overfeeding, inhibits the release of reproductive and thyroid hormones and lessens the immunity (Heymsfield S.B., 1996).

Plasma leptin concentrations were measured in 204 obese and normal weight subjects aged 18-80 years. The patients were having no medical and surgical illness. The concentrations were measured by using RIA and full-length human recombinant leptin as a standard (Ahima R.S., 2011). The fasting levels observed were between 1.2-97.9 ng/ml. The statistical results showed that there was a high correlation between plasma leptin concentration and percent body fat ($r = 0.710$; $P<0.0001$). The leptin concentration was 3 times higher in women as compared to men. In 5 obese subjects, plasma leptin was reduced by 26% who consumed 1000 calories diet for 10 days ($P=0.004$). This shows that there is a link between increasing adiposity and continuous rise in circulating leptin (Flier J.S, 1998, p. 1450).

The gene that encodes for obesity is the ob gene. Leptin deficiency is caused by a missense mutation in the ob gene and it causes severe obesity (Welt C.K., 2004, p. 890). There is low dose leptin anorexigenic agents that are useful in the treatment of human obesity. As a result of reduced circulating leptin, there is a decrease in energy expenditure and hunger is increased (Farooqi I.S., 2002, p. 994).

In the general population, the partial leptin deficiency is not rare (R E Ostlund & R Gingerich, 2004, p. 1094). Leptin deficiency is linked with low numbers of T cells and irregular T cell proliferation. These defects can be altered by leptin therapy (Oral E.A., 2002, p. 3947). For energy homeostasis in mammals including mice and humans, the adipocyte-derived hormone leptin is very important (Boozer C.N., 2001, p. 4532).

Leptin signaling is associated with the JAK-STAT Pathway (108). The release of Neuropeptide Y is the component of the pathway and it increases during fasting. If any of the components of the leptin signaling pathway are missing then this signals for less food intake. The expression of the leptin gene is associated with a signaling pathway (Begriche K., 2008, p. 185).

The activity of leptin is also associated with its receptor. The binding receptor is known as leptin receptor (LEPR), a cytokine receptor. It has six different isoforms which are formed as a result of alternative splicing. LEPR is important for leptin signaling. A mutation in

the leptin receptor alters LEPR signaling which results in obesity (Farooq IS, 2009, p. 6044).

4. Availability and non-availability of Leptin lead to other diseases

It has been observed that low or high amount and non-availability of leptin leads to many diseases and disorders such as autoimmune diseases are usually due to low amount of leptin. Many other diseases such as stress is also related to the low amount of leptin. Leptin therapy is nowadays used for the treatment of diseases such as:

(A) Autoimmune diseases

There is an association between leptin, immune diseases, nutrition level and body's metabolism. The optimum level of leptin is critical for the perfect working of immune system because it has proinflammatory characteristics (Hakansson-Ovesjo ML., 2008, p. 56).

Recent researches have shown leptin to be involved in the initiation and development of encephalomyelitis, an autoimmune disease associated with the inflammation of central nervous system (Licinio J., 2003, p. 202). Women are more prone to autoimmune diseases as compared to men this is because the level of leptin in the CSF of women is more as compared to men which cause many diseases such as systemic lupus erythematosus, atherosclerosis, and multiple sclerosis, ulcerative colitis (Nanjappa V., 2011, p. 78).

Fasting is an important factor to reduce autoimmune disorders because fasting leads to decreased leptin in the body that results in decreased autoimmune diseases. Some diseases are also caused by the decreased level of leptin such as ANCA associated vasculitis. This can be treated by giving leptin replacement therapy to the patients (Kimber W, 2008, p. 556).

(B) Central nervous system diseases

It has been observed that leptin receptors are more abundant in the master gland of the brain and regulate many of the pathways there such as JACK/STAT pathway, MAPK pathway, mTOR pathway. Leptin receptors are also observed to initiate the main signaling pathways (Mattioli B & Quaranta MG, 2005, p. 57).

Figure 3: Signaling pathways of leptin and effects on central nervous system diseases.

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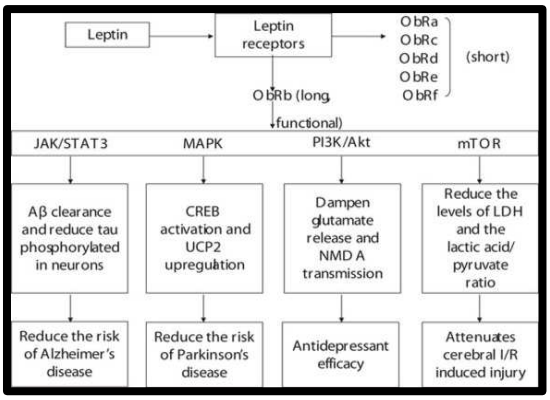

i. Alzheimer's disease

It is a neurodegenerative disorder resulting in memory loss and collapses of a synapse which results in the loss of cerebral and social abilities gradually leading to the death of brain cells (Mattioli B & Quaranta MG, 2005, p. 67).

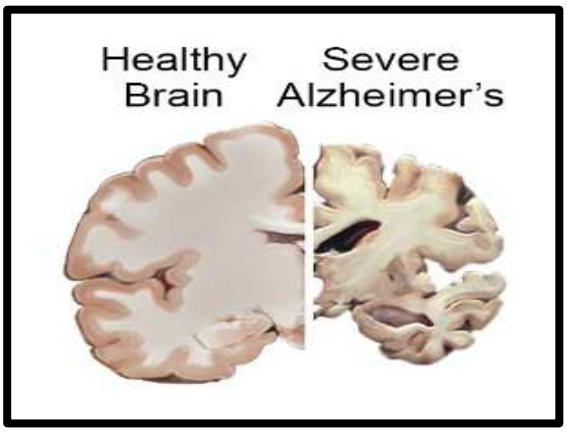

Figure 3.1: Comparison of healthy cells and cells affected with Alzheimer's disease.

(Retrieved from: https://www.rfsafe.com/radiation-cell-phones-cause-uks-100-increase-early-dementia-starting-30/)

Leptin receptors are very much susceptible to Alzheimer's disease and it has been observed that more amount of leptin reduces the risk of Alzheimer's disease by preventing the

accumulation of Aβ. As there is a low level of leptin in the patients affected with the AD. It also prevents the accumulation of phosphorylated tau due to which we can use it as an Alzheimer's therapy. JAK/STAT3 pathway is involved to reduce the risk of the AD (Leinninger GM & Cappellucci LA, 2011. P. 68).

i. Parkinson disease

It's a disease which affects the facial and skeletal muscles and causes them stiff gradually results in loss of motor activity.

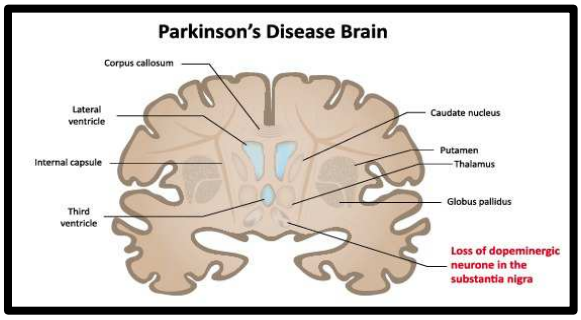

Figure 3.2: Brain of a patient affected with Parkinson disease.

(Retrieved from: https://www.flagstaffbusinessnews.com/living-parkinsons-disease/)

It is also associated with MAPK and CREB regulation and UCP2 up-regulation which is closely linked with Parkinson disease. So leptin therapy of such patients is very effective (Fiszer U & Jeske W, Jethon M, 2010).

i. Depression

It is the illness which affects the patients each and every activity. It is a mental illness leading to many other illnesses such as memory loss. Now a days, it is the major cause of death in many developed countries. Leptin acts as an antidepressant in mice affected with depression by activating ObRb in the hippocampus. It involves the P13K/AKT pathway for damping glutamate release and NMDA transmission for antidepressant efficacy (Lu X & O'Malley KL. 2014).

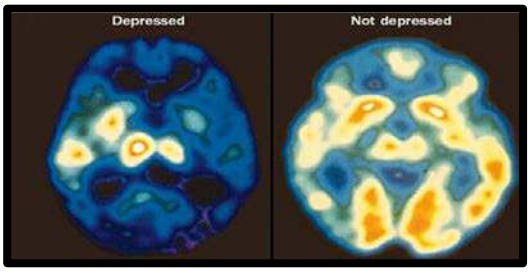

Figure 3.3: Comparison of the normal and depressed brain.

(Retrieved from https://www.medicinenet.com/depression/article.htm)

i. Brain Stroke

It is the blockage of the blood towards the brain may be due to the bursting of vessel or deposition of fats which may lead to death (Guo M & Chua SC, Zhang W, 2012, p. 123).

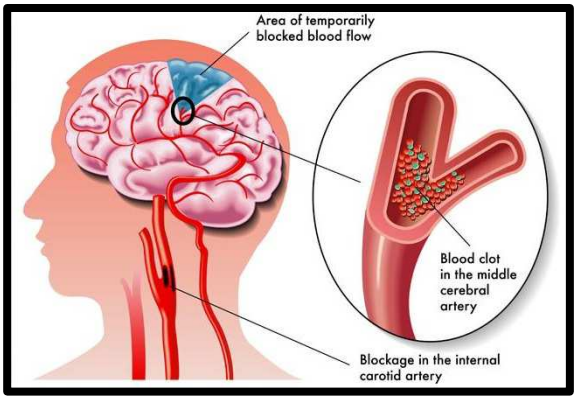

Figure 3.4: Image showing the blockage in the artery.

(Retrieved from: https://4rai.com/blog/these-3-imaging-tests-can-help-determine-your-risk-of-stroke)

It has been observed that males with higher levels of leptin become the victim of stroke more and faster than females (Bado A & Bortoluzzi M. N, 1998, p. 33). Obesity and overweight are increasing day by day and with the increase in weight, there is an increase in leptin. Recent studies show that the presence of leptin decreases the septate and pyruvate ratio and leads to acidosis. There is the variation in STAT 3 phosphorylation in the rat infected with cerebral stroke so leptin can be used as therapy for such patients but the practical application of such therapy is still under study (Savopoulos C & Hatzitolios A. 2011, p. 211).

5. Conclusion

Leptin is a protein hormone responsible for energy conservation in the body. It is used as anti-obesity hormone due to its role in decreasing appetite and aiding in weight loss. The present study aims to evaluate the role of leptin hormone in regulating various body functions, negative effects of leptin imbalance and the possible treatments available for correcting these disorders, specially the leptin induced obesity. It has been suggested that mutated leptin Ob gene leads to severe obesity as well as various other disorders such as central nervous system disorders and autoimmune diseases. Leptin has also been observed to be related to many other metabolic functions e.g. it regulates the synthesis of thyroid hormones, increases heart rate, decreases the insulin secretion, and maintains the mass of the bone. It also regulates menstruation cycle and activates the immune system. Dietary adjustments and physical activity can help restore the normal leptin functioning. Leptin replacement therapy has been observed to contribute to a great degree towards weight loss among obese cases by adjusting normal immune system and hormonal functioning. It is important to look into the detailed pathophysiology of leptin resistance which as of yet is unclear. Therefore, more research is required to understand the working of leptin ob gene and its relationship with health defects and also to discover the most effective approach for reversing these defects.

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