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Review Article

Leptin and its receptor – A review

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ABSTRACT

Leptin is a polypeptide hormone, mainly secreted by the adipocytes that regulates the energy expenditure of the body. Since its discovery, various researches have been conducted to find out about its role in human body. Leptin receptor (Ob-R) is a membrane spanning receptor with six different isoforms. The long isoform of leptin receptor is the major form found in various tissues of the human body such as brain, lymphocytes, stomach, intestine, pancreas, liver and placenta. This article discusses about the structure of leptin receptor, its various locations in the human body, effects due to the deficiency of leptin receptors and its evolving therapeutic applications.

1. Introduction

Leptin, a hormone mainly secreted by the adipocytes was discovered by Douglas Coleman and Jeffrey Friedman in the year 1994. The hormone is a 167 amino acid product and is a major regulator of energy homeostasis in mammals. It regulates energy expenditure by modulation of glucose and fat metabolism in the body. It is positively correlated with the amount of body fat. The level of leptin usually fluctuates with the amount of food intake. The major factors promoting leptin secretion include obesity, overfeeding, glucose, insulin and glucocorticoids. The factors inhibiting the secretion of leptin hormone are fasting, lean body weight, catecholamine, thyroid hormones and adrenergic agonists.[1] Leptin plays a major role in energy homeostasis, neuroendocrine function,[1] metabolism, immunity,[2] growth and remodeling of lungs,[3] growth and maturation of fetus.[2] The emerging recombinant human leptin also has several therapeutic applications. In this review, we summarize the structure of leptin receptors, gene encoding them, methods of detection of leptin receptors, various locations of leptin receptors, the physiological and pathological role of leptin, features of congenital leptin deficiency and recent advancements in the therapeutic applications of leptin.

2. Materials and Methods

2.1. Search engine

PubMed and Google scholar.

2.2. Inclusion criteria

Articles included in this review were related to the structure and localization of leptin receptors and the various methods applied for its detection. Articles in English language and human studies were included.

2.3. Exclusion criteria

Studies involving animal subjects and articles other than the English language were excluded in the study.

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3. Structure of Leptin Receptor

The leptin receptor, a member of class-I cytokine receptor family has six isoforms. The receptors are membrane-spanning or transmembrane protein with an extracellular and intracellular domain. The receptors are broadly classified into three categories: long, short, and secretory based on its structure.[4]

The Ob-R (Leptin receptor or Obesity receptor) is expressed in six isoforms. It consists of gp130 subunit of IL-2R, IL-3, IL-4, IL-6, IL-7, LIF (Leukemia inhibitory factor), G-CSF (granulocyte – colony stimulating factor), growth hormone, prolactin and erythropoietin receptors.[5] The Ob-R expresses three domains: extracellular, transcellular, and intracellular. The receptors are classified into long and short isoforms based on the length of the intracellular domain. The extracellular domain consists of 816 amino acids and is located in the N-terminus of the protein. All the Ob-R isoforms, except the Ob-Re isoform, has a transcellular domain consisting of 34 amino acids. The Ob-Rb isoform (long isoform) consists of an intracellular domain that has 303 amino acids in the carboxy terminus of the protein. The short isoforms (Ob-Ra, Ob-Rc, Ob-Rd and Ob-Rf) consists of a shorter intracellular domain of 32-40 amino acids. Even though the length of the amino acid chain differs in the long and short isoform, the sequence of the first 29 amino acids remains the same. A sixth Ob-R isoform (Ob-Re) is devoid of the transcellular and intracellular domains and is secreted as a soluble leptin receptor.[6] These are mainly produced by the proteolytic cleavage of the extracellular domain of the other isoforms of the leptin receptor. These soluble leptin receptors are capable of differentiating between the free and bound leptin and serve as the leptin binding protein in the human plasma.

Leptin is encoded by Ob gene. The human Ob gene consists of approximately 20 kilobases and contains three exons and two introns in between them. This gene is situated in human chromosome 7q31.3.[7]

4. Methods of Detection of Leptin Receptor

Various methods are employed to detect leptin and its receptors in various tissues of human body. The targets for detection are mRNA coding for leptin, mRNA expression of leptin receptor isoforms, leptin protein expression and leptin receptor isoform expression. The mRNA expression is most commonly detected by reverse transcriptase – polymerase chain reaction (RT-PCR).[8] The protein and the receptor expression is detected by immunohistochemistry using specific antibody against leptin and the receptor isoforms.[9] The receptor isoforms are also detected with the western blot method using specific receptor anti-serum. In a study conducted by Aparacio et al., the Ob-R expression was also detected by flow cytometry.[8]

5. Localisation of Leptin Receptors

Using the various above discussed methods leptin protein and its receptor expression were found in various tissues of human body. Leptin initially was thought to be a hormone which is just involved with food intake and energy expenditure. But as a lot of researches were conducted, leptin was isolated and localized in many tissues of human body providing evidence to the diverse role of leptin in human physiology. Even though it is a well-known fact that leptin is primarily produced by the adipose tissue, a lot of researches happening in the recent decades have thrown light over the other tissues secreting leptin and various tissues with its receptors.

Marta E. Couce et al. localized the leptin receptor in the human brain using immunohistochemistry and western blotting. They found that the leptin receptor was expressed both in the neuronal and non-neuronal compartments. Within non-neuronal compartments, the receptors were highly expressed in choroid plexus epithelium, small vessel walls and at the apical surface of ependymal cells. Neuronal components with positive immunostaining for leptin receptor include several hypothalamic nuclei (arcuate, suprachiasmatic, mammillary, paraventricular, dorsomedial, posterior and supraoptic), cerebellar Purkinje cells, neurons of nucleus basalis of Meynert and medullary inferior olivary nuclei.[10]

Elizabeth Papathanassoglou et al. investigated the expression of leptin receptors in lymphocytes. Their data suggests that macrophages, B and T cells express leptin receptors at low levels in resting state. When activated, the expression of leptin receptors is higher in macrophages than with T and B cells.[11]

H Mix et al. demonstrated the leptin and its receptors in human stomach. These receptors were localized in the gastric epithelial glands with chief cells as its primary source. Some studies indicate that the expression of leptin receptors were upregulated in patients with H.pylori infection. These gastric leptin is suggested to have both paracrine and endocrine effects through portal vein and central nervous system via stimulation of vagus nerve.[12]

Flavio Mergio et al. found that leptin and its receptor Ob-R are expressed heterogeneously in the large intestinal epithelial cells and lamina propria.[13]

Many other recent studies have found the expression of leptin and its receptor in various tissues of human body such as pancreas, liver (kupffer cells, hepatic stellate cells and sinusoidal endothelial cells)[14] and placenta.[15] Leptin also has many effects on the physiology of human body. It plays a role in the carbohydrate metabolism, menstrual cycle of female, immune system, regulation of blood flow, vasodilation in endothelial cells and bone formation.[16]

6. Congenital Leptin Receptor Deficiency

Leptin receptor deficiency is a rare endocrine disease. These patients usually have extreme early onset and clinical features of genetic obesity disorder and/or positive family history for extreme obesity. Other clinical features include hyperphagia, central hypothyroidism, growth hormone deficiency, hypogonadotropic hypogonadism, hyperinsulinemia and frequent infections. Mortality in early childhood is reported due to infectious causes.[17] Many researchers reported resolution of central hypothyroidism and hypogonadism at the onset of puberty. However, the number of cases are too low to draw a conclusion on this phenomenon. Many patients with leptin receptor deficiency have not yet been recognized due to either non availability or inaccessibility to genetic testing.[18]

7. Therapeutic Applications of Leptin

Leptin that is currently used for therapeutic purposes is recombinant leptin. It is used as leptin replacement therapy in individuals with congenital leptin deficiency. Leptin is increasingly explored as an option of treatment of obesity and its related complications. It is also used in reduction of triglycerides. Many researches are being conducted in using leptin as a therapeutic approach for diabetes, hypothalamic amenorrhea and to resolve anovulation.[19]

8. Conclusion

We have discussed the structure and various locations of leptin receptors in this review. This article also briefly describes the physiological impact of the leptin protein in human body. Recent studies have also thrown light on the involvement of leptin and its fluctuating levels in various pathological conditions. Further more studies are required to guide the usage of leptin as a therapeutic option in various disease processes.

9. Source of Funding

None.

10. Conflict of Interest

None.

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