Role of Leptin in Obesity

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Abstract

Obesity has been the problem in the societies of developing and developed world. Some diseases caused by obesity. To overcome of those diseases it is necessary to control obesity. Most of the articles showed that the Leptin may be a vital tool to fight against obesity because it is the anti-obesity hormone. By using leptin therapy may be possible to prevent obesity and diseases like hypertension and diabetes mellitus before their occurrence.

Keywords: Leptin; Hypertension; LEPR (Leptin Receptor); Obesity; Neuroendocrinology

Introduction

Leptin is a hormone that comes from Greek word meaning "thin" it is also known as "Ob gene" that is located on chromosome number 7. Cytogenetic location is 7q31.31 and consists of three exons and two introns that span 20 kilobases (kb) of DNA. Main role of leptin is to achieve an energy balance in the body [1]. Leptin binds to receptors in brain and performs several actions that may prove that leptin is important in treating obesity [2]. This hormone is produced by the adipose tissue, mainly by the white adipose tissue of the human body; it is comprised of 167 amino acids. The amount of leptin circulating in the body is proportional to the amount of fat of an individual [3]. Researchers thought that leptin would be the key in controlling obesity. But research revealed that if greater amount of leptin release then it is less effective in the brain for controlling hunger and food intake. The result is uncontrolled feeding, leading to greater food intake and fat storage [4]. It is a 16-kDa circulating hormone that regulates energy homeostasis via hypothalamic neuronal pathways expressing the leptin receptor [1]. The deficiency of leptin or leptin receptor in humans results in extreme obesity and implicates leptin-mediated signaling in the regulation of food intake, energy expenditure, reproductive, thyroid and immune functions [2]. Level of leptin is positively correlated with fat mass, being increased in obesity [4,5]. But some studies suggest that leptin may have a stimulating effect on fat oxidation in obese subjects [6]. Leptin is also produced in fewer amounts in the placenta and probably in the stomach [4]. It is reported that large fat cells produce more leptin than small ones. Serum leptin concentrations are highly correlated with body fat content in newborn infants, children and adults [6]. First genetic defect of leptin described in 1950s as the spontaneous mutation in Ob/Ob mice that causes a severe obese phenotype due to overeating and decreased energy expenditure. Leptin gene was named ob and the obese mice carrying the mutation were called ob/ob mice. 3 Leptin Receptors (LEPR) are highly expressed in the hypothalamus part of brain which is important in regulating body weight, in T lymphocytes and vascular endothelial cells. Leptin inhibits food intake by central action on the hypothalamus. Its functions are quite pleiotropic. It is implicated in a variety of cellular processes, including the modulation of immune cell function. Leptin is structurally related to the long chain helical cytokine family, which includes IL-2, IL-12, and growth hormone. Main channel of this gene is JAK/STAT [7]. Leptin acts via two groups of arcuate neurons which are located in the hypothalamus region of the brain. First group expresses Agouti-related peptide and Neuropeptide Y (NPY) and second group expresses Pro-Opio-Melanocortin (POMC) and Cocaine and Amphetamine-Related Transcript (CART) [8].

What is Leptin?

Leptin is a hormone that was largely unknown to the scientific community before 1994. Role of leptin is to maintain energy balance by regulating food intake and calorie burn rate. As the amount of fat stored in cells, leptin is secreted into the bloodstream and signals that make you eat more or less. Actually leptin is a 16-kDa protein. It is secreted by adipocytes and dominantly has major role in the body weight regulation by maintaining a balance between food intake and expenditure of energy. This gene has several other endocrine functions. Most important functions are the regulation of immune and inflammatory responses as well as in angiogenesis and wound healing. It is observed that leptin is the important hormone that is derived from white adipose tissue [9,10]. Leptin discovered more than 10 years ago, its function is to decrease food intake and increase nerve activity to both thermogenic and non-thermogenic tissue. It was believed that leptin is an anti-obesity hormone. Leptin plays major role in the development of hypertension in obesity [11].

Leptin Regulation

Many hormones present in the body that upregulate or downregulate the level of leptin. Leptin is upregulated by insulin and cortisol and downregulated by catecholamines. In addition to these factors, tumor necrosis factor-α (TNF-α) also serves as a paracrine regulator to increase the secretion of leptin. Leptin also autoregulates its own expression by glucose and fatty acids also influence leptin expression [12].
Regulation of Energy Expenditure, Food Intake and Body Weight by Leptin

Leptin is an important component in the long term regulation of body weight. Recent studies with obese and non-obese humans demonstrated a strong positive correlation of serum leptin concentrations with percentage of body fat. It appears that as adipocytes increase in size due to accumulation of triglyceride, they synthesize more and more leptin. Leptin’s effects on body weight are mediated through effects on hypothalamic centers that control feeding behavior and hunger, body temperature and energy expenditure [13].

Pathways Involved in Leptin Production

JAK-STAT Pathway has great importance in leptin signaling. Studies indicated that in the hypothalamus region, leptin specifically activated STAT3 pathway [14]. Neuropeptide Y promotes feeding behavior in the body. Expression of Neuropeptide Y (NPY) will increase during fasting. Absence of the NPY failed to change body weight and feeding in normal mice. If any of the components missed in pathway then less food intake [15]. Pathways of the leptin gene have importance in its expression [16].

Leptin Receptors (LEPR)

Activity of leptin is dependent on its binding with its receptor, known as leptin receptor (LEPR). LEPR belong to gp130 family of cytokine receptor. After the alternative splicing of LEPR, six different isoforms were formed. These isoforms are LEPRa, LEPRb, LEPRc, LEPRd, LEPRe and LEPRf. Out of these six, LEPRb is the important and longest isoform that has the capacity of strong signaling as compared to others. Defect in leptin signaling cause severe obesity [17]. First missense mutations which were present in the leptin receptor (LEPR) were reported. These mutations disrupt LEPR signaling. Mutations associated to human obesity were involved in structural as well as functional relationships within the LEPR [18].

Leptin in Obesity

Leptin is a neurotransmitter expressed in the brain. This neurotransmitter signals to the brain mainly in the hypothalamus that when a person stops to eat for maintaining his Body Mass Index. It has been observed that lab mice have a polymorphism in the leptin gene. Mutations in this gene prevent to manufacture the functional leptin protein. Due to less leptin expression, mice become morbidly obese. Another strain has a mutation or polymorphism in the gene encoding for the Leptin Receptor (LEPR). In this case, signal of the leptin is not received by the brain or the hypothalamus. So due to signal disruption or mutations in the leptin receptor, mice become obese (www.loop.com/%7Ekbrentzman/obesity/genetics.html). A study involves comparison of obese and lean individuals with respect to leptin level. Experiments included 25 obese and 25 severely lean individuals. Sequence of leptin gene was analyzed by using SSCP, heteroduplex analysis and automated Sanger sequencing. Result suggested that in Pakistani population leptin gene may not be a major cause for obesity and leanness. Until know six mutations have been reported and these mutations are listed below in Table 1.

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Mutations</th>
<th>Individuals</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>p.Gly133fsX145</td>
<td>Two Pakistani cousins</td>
<td>Montague et al. [2]</td>
</tr>
<tr>
<td>2.</td>
<td>R105W</td>
<td>4 members from Turkish family</td>
<td>Strobel et al. [3]</td>
</tr>
<tr>
<td>3.</td>
<td>N103K</td>
<td>2 Egyptian children</td>
<td>Mazen et al. [4]</td>
</tr>
<tr>
<td>4.</td>
<td>L72S</td>
<td>14 years old female child</td>
<td>Fischer-Posovszky et al. [22]</td>
</tr>
<tr>
<td>5.</td>
<td>p.Leu161fsX170</td>
<td>1 Obese child from Pakistan</td>
<td>Fatima et al. [8]</td>
</tr>
<tr>
<td>6.</td>
<td>c.104_106delTCA</td>
<td>1 Obese child from Pakistan</td>
<td>Fatima et al. [8]</td>
</tr>
</tbody>
</table>

Table 1: Six pathogenic mutations in chronological order.

Diseases Due to Obesity

Some diseases are associated with obesity such as certain types of cancers, type II diabetes, heart diseases, obstructive sleep apnea and osteoarthritis [19]. Some factors by which obesity is commonly caused include excessive food intake, less physical activity and abnormalities in genetics as well [20,21].

Leptin Therapy

Leptin therapy reversed endocrine as well as metabolic alterations associated with leptin deficiency [22]. Leptin deficiency was related with less numbers of T cells, CD4 and defective T cell proliferation. These reductions were reversed by leptin therapy [23]. Leptin replacement therapy at physiological concentrations after removal of high-dosage leptin not worked properly weight regain and hyperphagia was due to deficiency of leptin [24]. Leptin replacement therapy will be very useful for the patients of congenital leptin deficiency. Leptin has also been used for the treatment of other forms of energy loss e.g. anorexia nervosa [25]. It was found that immune function changed during leptin replacement. Congenital leptin deficiency was evaluated in a 5 year old boy. Boy was evaluated before two weeks and after six weeks of leptin therapy. After that treatment, humoral and cellular immunity was detected by measuring levels of immunoglobulins and by the analysis of lymphocyte in response to mitogens, respectively [26].

Neuro-Endocrino-Biological and Obesity

Scientists reported that obesity and overweight may be associated with cognitive problems. Both obesity and overweight may share “neuroendocrinobiological roots” in common cerebral areas. In this study scientist collected 898 samples from school children. Age ranges of all the samples were 6 to 13 years. Intellectual level and specific
cognitive profile was done with the help of different experiments. Results showed significant system difference in intelligence levels in different BMI subgroups calculated by Wechsler Intelligence Scale for Children-revised (WISC-R). According to regression analysis BMI is the only variable that is significantly related to intellectual level. So, to check out intellectual level in obese and overweight children a routine neurocognitive assessment is recommended [27,28].

Conclusion

Obesity has been the problem in the societies of developing and developed world. Some diseases caused by obesity. To overcome of those diseases it is necessary to control obesity. Most of the articles showed that the Leptin may be a vital tool to fight against obesity because it is the anti-obesity hormone. By using leptin therapy may be possible to prevent obesity and diseases like hypertension and diabetes mellitus before their occurrence.

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