LEPTIN: A POTENT SUBSTANCE TO COMBAT DIABEES MELLITUS

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Summary

Leptin is an adipocyte hormone coded by the obesity gene located on chromosome 7 in humans. Mutations in the obesity gene and defect in leptin receptor caused obesity in mice and humans, and type2 diabetes mellitus in mice. Obesity is a known risk factor for type2 diabetes mellitus. Leptin prevents obesity, enhances insulin signal transduction and therefore insulin sensitivity, enhances glucose uptake by the liver cells and skeletal muscles, and inhibits hepatic glucose output, acting through the neurohormonal circuit, the leptin-melanocortin circuit, ATP sensitive potassium channels and insulin-stimulated receptor substrate (IRS) phosphorylation pathway. Leptin has been successfully used to treat obesity and type2 diabetes in mice, and obesity in man. It is possible that it can be useful in the treatment of diabetes in man. Improved understanding of the mechanism by which leptin affects blood glucose level may give insight into possible use of this substance in the control of diabetes mellitus in man.

Key words: Leptin, Obesity, Type2 Diabetes, Treatment.

Introduction

There are about 40 neurotransmitters in the brain known to control behaviour. Twelve of these neurotransmitters, including leptin, are known to control eating habits in a variety of ways. Leptin is a 146-amino acid polypeptide hormone produced by the adipocytes and coded by the obesity (OB) gene located on chromosome 7 in humans (1). It modulates energy balance and metabolism and plays significant, if not primary, roles in heart disease, obesity, diabetes, osteoporosis, autoimmune diseases, reproductive diseases, and perhaps, the rate of aging itself (2) Mutations in the OB gene affect the expression of leptin, leading to these disease conditions especially obesity, infertility and diabetes in laboratory mice. Laboratory mice that have mutation on the OB gene, which prevents the manufacture of leptin, developed morbid obesity (3), indicating that they never got leptin signal to stop eating. Another strain of the mice with a mutation in the gene that code for the leptin receptor, so that even if leptin is produced, its signal is never received by the brain, also became obese. There are two types of mutations that are known to affect the OB gene.

The first is the nonsense mutation, resulting to the production of a non-functional protein. The second mutation affects the promoter regions resulting in no transcription and no protein at all. In humans, mutations in OB gene caused some severe cases of early onset obesity and diabetes (4). Other less severe varieties of human obesity are not caused by mutation, but by an altered regulation or resistance to the action of leptin. Reduced leptin production or fewer receptors may also account for those who are overweight but not obese (5).

Diabetes mellitus (DM) is a group of disorders of carbohydrate metabolism in which glucose is under-utilized, producing hyperglycaemia. It is mostly caused by autoimmunity, obesity, infections and other disease conditions affecting the endocrine functions of the pancreas, and usually characterized by such primary symptoms as polyuria, polydipsia and polyphagia (6,7). DM is broadly divided into type1 (insulin-dependent) and type2 (non-insulin dependent) diabetes mellitus. In America, 90% of diabetic cases are of type2, probably resulting from over 60 million obese Americans (8). Type2 diabetes and obesity are closely related; hence in America, being overweight increases the risk of type2 diabetes seven folds (2). Fortunately, leptin, which is known to have effect on obesity, also has regulatory effect on blood glucose and insulin (9). Its deficiency or resistance to its presence is known to cause obesity (3), predisposing the affected individual to diabetes. Based on this, and because of its regulatory role on blood glucose and insulin, leptin seems to be a potential tool for the control and/or treatment of diabetes, particularly type2 diabetes.

Biochemistry of Leptin

Studies (10) have shown that leptin is a member of the helical cytokine family with no detectable sequence homology between its members. The exact structure of leptin is not yet certain because studies (5,10) have shown that the primary structure or amino acid sequence showed no homology with any other protein in the data bank, making it difficult to predict a three-dimensional structure. However, threading technique showed that leptin's folding pattern is compatible with the helical cytokine, being mostly related to interleukin-2. Again, wild type leptin can aggregate and therefore could not be crystallized, making the use of X-ray crystallography for structure elucidation difficult. However, Zhang (5) was able to get mutant leptin crystallized. This mutant, which has glutamic acid at position 100 substituted by typtophan, has comparable activity as leptin. This is called leptin E-100.

Mechanism of Leptin Action

The most studied mechanisms of leptin action are the neurohormonal circuit and the leptin-melanocortin circuit (11). The other mechanisms are those by which leptin acts in the pancreas and the liver to regulate insulin and blood glucose level respectively. The neurohormonal mechanism has three systems – (a) the system that generates hormonal signals from the adipose tissue (leptin), pancreas (insulin) and stomach (ghrelin), (b) the central processing unit located peripherally in the hypothalamus which integrates the afferent signals, and (c) the effector system which carries out orders from the hypothalamic nuclei in the form of feeding behavouir and energy expenditure. Among the different signals, insulin and leptin exert long-term control over the energy cycle by activating catabolic circuits and inhibiting anabolic pathways. By contrast, ghrelin is predominantly a short-term mediator produced by the stomach. Ghrelin levels rise sharply before every meal and fall promptly when the stomach is filled. In fact, it is thought that the success of gastric bypass surgery in massively obese individuals may relate more to the associated suppression of ghrelin levels than to an anatomic reduction in stomach capacity. In summary, when sufficient energy is stored in adipose tissue and the individual is well fed, afferent signals (insulin, leptin and ghrelin) are delivered to the central processing units in the hypothalamus. Here, the adiposity signals inhibit anabolic and activate catabolic circuits.

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The effector arms of these central processing circuits then impact on the energy balance by inhibiting food intake and promoting energy expenditure. This in turn reduces the energy stores, thus blocking adiposity signals. Conversely, when energy stores are low, the available anabolic circuits take over at the expense of the catabolic circuit, to generate energy stores in the form of adipose tissues.

In leptin-melanocortin circuit, the most critical receptors for regulation are expressed in the arcuate nucleus of the hypothalamus. There are two major types of neurons in this locus that bear leptin receptors - the first order neurons and the second order neurons. The first order neurons, which are the initial target of leptin are activated by leptin signals and exert catabolic effects, mainly through the secretion of melanocyte-stimulating hormone (MSH). In anabolic pathway, the first order neurons make monosynaptic connections to the second order neurons, which express oraxogenic peptides – melanin concentrating hormone, and oraxins A and B. The neuropeptide released from the first order neurons binds to its receptor on the second order neurons, and thus transmit feeding signals. Such signals are attenuated when leptin is in excess and are activated by low level of leptin. Another neuron – melanocortin-4 receptor (MC4R) neurons, are mediated in part by the release of thyrotropin-releasing hormone (TRH), which activates the thyroxin axis through the anterior pituitary. TRH does not only increase thermogenesis via secretion of thyroxin, but also suppresses appetite. Corticotrophin-releasing hormone (CRH), which is another important product of MC4R neurons, induces anorexia and also activates the sympathetic nervous system. A subset of MC4R neurons projects to sympathetic motor output area. Fibre in this area innervates brown adipose tissues rich in beta-adrenergic receptors. When these receptors are stimulated, they cause fatty acid hydrolysis and also uncouple energy production from storage, thus burning out the fats.

Obesity and Type2 Diabetes

Leptin is one of the major hormones involved in energy balance and hence prevents obesity. In America, overweight increases the risk of type2 diabetes by seven folds (2). More than 18 million people in the United States have diabetes and about 90% of them are of type2 (8). Most of these cases of type2 diabetes are known to be as a result of living a sedentary lifestyle; being overweight and over-eating. The link between obesity and diabetes is mediated via effects of insulin resistance (11). Insulin resistance is also present even in simple obesity unaccompanied by hyperglycaemia, indicating a fundamental abnormality of insulin signalling in states of fatty acid excess. The risk for diabetes therefore increases as the body mass index increases. However, it is not only the absolute amount, but also the distribution of body fats that has effect on insulin sensitivity. Therefore, central obesity is more likely to be linked with insulin resistance than peripheral fat deposits. The mechanism of this adipo-insulin axis is based on the fact that intracellular triglycerides and products of fatty acid metabolism are potent inhibitors of insulin resistance states, and adipokines such as leptin, resistin and adiponectin are dysregulated in obese individuals, leading to insulin resistance (11,12).

Also in obesity, leptin signal is blocked and as such, the brain is not aware of how much fat is in the fatty cells. The metabolic signal assumes that there is starvation and slows down thyroxin activity, and at the same time increases appetite, thus ensuring weight gain. At a time, the urge and craving to eat becomes uncontrollable. This is a condition of leptin resistance or non-recognition. The uncontrollable eating in most cases leads to obesity and possibly diabetes (also characterized by polyphagia – abnormal increase in eating). Hence the influence of leptin on eating habit will ultimately be extended to control of diabetes. There are four basic mechanisms by which leptin can affect diabetes.

Leptin can reverse hyperinsulinemia. There is a link between leptin and beta cells of the pancreas, which produce insulin. In a study (13), it was found that insulin levels of normal mice dropped when they had not eaten recently while mice with mutant genes developed hyperinsulinemia – a risk factor for type2 diabetes. This later condition disappeared when the mutant mice were treated with leptin, indicating that leptin directly reduces insulin secretion in the beta cells of the mice. This observation is particularly of interest since in humans, fasting hyperinsulinemia is a risk factor for type2 diabetes, as well as for cardiovascular disease. Leptin suppresses insulin secretion by interacting directly with receptors on the beta cells, thereby activating an ion channel. This channel called an ATP-sensitive potassium channel is known to be a key component in the process by which the pancreas secretes insulin in response to increased blood glucose level. Leptin is also a part of a communication system between the pancreas and the body's fat stores (13). A problem in that communication system could be a key step in the development of type2 diabetes. Thus, the successful use of a novel gene therapy technique to treat type2 diabetes in mice led to the proposal that leptin or leptin-sensitizing drugs can be used in the treatment of type2 diabetes in obese individuals (8).

Leptin can enhance insulin signal transduction. The relationship between leptin and insulin signalling helps to elucidate the insulin resistance and cardiovascular complications that accompany diabetes in obese patients. Mazumber et al (14) showed that altered insulin action in ob/ob cardiomycetes was responsible for impaired insulin-stimulated glucose uptake. Leptin enhances the phosphorylation of insulin receptor and activation of phosphatidylinositol-3-kinase (PI3K). Activated PI3K phosphorylates membrane phospholipids, producing phosphatidylinositol-3,4,5-triphosphate (PIP$_3$) which in turn activates the enzymes – protein kinase B (PKB), PIP$_3$-dependent kinase (PDK), some isoforms of protein kinase C (PKC) and small ribosomal subunit protein 6 kinase (P70s6K). The total effect of these is to enhance glucose uptake via the translocation of GLU-4 and also inhibition of hepatic glucose output by phosphorylating and/or inhibiting glycogen synthase kinase 3 (GSK3). In addition, leptin deficiency affects insulin-mediated substrate metabolism, leading to impaired insulin-stimulated glucose metabolism (14). However, the signalling pathways by which leptin promotes insulin-mediated glucose metabolism are not yet completely understood. Probably, it may lower fatty acid pools to promote glucose oxidation. Insulin and leptin signals converge in the hypothalamus, fat cells and beta cells. A study (15) using specific kinase inhibitors revealed that phosphatidylinositol-3-kinase (PI3K), which is common to both signalling pathways, was the point of convergence.

Leptin can enhance glucose uptake. Leptin increases the phosphorylation of microtubule-associated protein kinase (MAPK), Ras protein and protein kinase B (PKB) in the liver and the adipose tissues (16). Phosphorylation of the MAPK enzymes activates a cascade of reactions, which activate protein phosphatase-1. Active phosphatase-1 then dephosphrylates and activates glycogen synthase, thereby decreasing blood glucose level. The protein phosphatase-1 also dephosphorylates and inactivates glycogen phosphorylase, thus inhibiting glucose output via glycogenolysis. The exact mechanisms by which leptin inhibits hepatic glucose output and enhances hepatic glucose uptake are not yet very clear.

Leptin can reverse insulin resistance. Studies (9) had shown that leptin reversed the insulin resistance associated with diabetes and obesity in mice. The underling mechanisms are still unclear, but it is known that leptin enhances insulin signal transduction, reduces pancreatic secretion of insulin and reduces blood free fatty acids (17).

Conclusion

Leptin has been successfully used to treat lipodystrophy in mice (9). The successful treatment was found to be due to enhanced glucose uptake by the liver, improved insulin sensitivity, reversal of insulin resistance, increased insulin signal transduction, up-regulation of the enzymes involved in glucose metabolism and decreased hepatic glucose output. Leptin has also been used to treat type2 diabetes that resulted from ob gene mutation in mice (8), and has as well been used to treat obesity in nine-year old girl who was homozygous for a frame-shift mutation in her ob gene (18). From the foregoing, it is likely that leptin will be of immense help in the treatment of diabetes mellitus in humans, either as a primary drug or a secondary chemical inducible by another drug.

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