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The Potential of Leptin Hormone in the Treatment of Diabetes Mellitus

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Abstract:

Leptin is a hormone secreted by adipose tissue and regulates energy homeostasis, neuroendocrine function, metabolism, immune function and other systems through its effects on the central nervous system and peripheral tissues. Although its award-winning discovery transformed the study of obesity more than 20 years ago, leptin's mechanisms have remained a mystery. Secreted by white fat cells, leptin acts in the brains of humans and many other animals as a satiety signal to reduce appetite and maintain stable weight and blood sugar levels. Dysregulation of leptin or its receptors results in ravenous appetite and extreme overeating (hyperphagia), obesity, and type 2 diabetes (which accounts for approximately 91% of diabetes diagnosed in adults in the U.S., affecting about 21 million people). Leptin supplements are generally ineffective for these disorders because, for unknown reasons, most obese individuals are leptin-resistant, and leptin's clinical applications remain limited despite extensive study. Due to its connection with insulin levels, Leptin has been a subject of particular interest with diabetes and cardiovascular pathology research. This review discusses the different theories on how leptin hormone can be a potential anti-diabetic treatment in both types of Diabetes Mellitus.

1. Introduction:

1.1. Structure and Function of Leptin Hormone:

Leptin is a 167-amino-acid peptide that is mainly expressed in white adipose tissue (WAT), but is also found in a variety of tissues including placenta, mammary gland, ovary, skeletal muscle, stomach, pituitary gland, and lymphoid tissue. Circulating leptin levels are directly in proportion to the amount of body fat, thereby reflecting the status of long-term energy stores. In addition, leptin levels fluctuate according to changes in calorie intake with a marked decrease during starvation. Leptin is secreted in a pulsatile manner, displaying a circadian rhythm with lowest levels at mid-afternoon and highest levels at midnight.

Leptin plays an important role in regulating energy homeostasis, neuroendocrine and immune functions, and glucose, lipid and bone metabolism. [(1)]

Because it comes from fat cells, leptin amounts are directly connected to an individual's amount of body fat. If the individual adds body fat, leptin levels will increase. If an individual lowers body fat percentages, the leptin will decrease as well.

Leptin is sometimes called the satiety hormone. It helps inhibit hunger and regulate energy balance, so the body does not trigger hunger responses when it does not need energy. However, when levels of the hormone fall, which happens when an individual loses weight, the lower levels can trigger huge increases in appetite and food cravings. This, in turn, can make weight loss more difficult.

1.2. Leptin Resistance and Deficiency:

When the body is functioning properly, excess fat cells will produce leptin, which will trigger the hypothalamus to lower the appetite, allowing the body to dip into the fat stores to feed itself. Unfortunately, when someone is obese, that individual will have too much leptin in the

blood. This can cause a lack of sensitivity to the hormone, a condition known as leptin resistance. Because the individual keeps eating, the fat cells produce more leptin to signal the feeling of satiety, leading to increased leptin levels.
Low levels of leptin are rare, but can occasionally occur. For a few patients, a condition known as congenital leptin deficiency keeps the body from producing leptin. Without leptin, the body thinks it has no body fat, and this signals intense, uncontrolled hunger and food intake. This often manifests in severe childhood obesity and delayed puberty. The treatment for leptin deficiency is leptin injections. [(2)]

2. Leptin Hormone as an Anti-diabetic:

2.1 Leptin Treatment in Type 1 Diabetes Mellitus:

2.1.1 The Problem with Insulin Therapy in Type 1 Diabetes Mellitus:

T1DM is caused by pancreatic β-cell loss a defect that results in the lack of the hormone insulin and a lethal catabolic outcome if untreated. As a classical endocrinological approach to treating an illness resulting from lack of a given hormone is to replace the hormone therapeutically. Unfortunately, this therapy does not restore normal metabolic homeostasis and as a result the life-expectancy and -quality of T1DM people is worse than the ones of normal subjects. In part, this is due to challenging morbidities of T1DM, as for example heart disease and hypoglycemia, both of which are thought to be caused by insulin therapy itself. Indeed, owing to insulin's lipogenic actions, this treatment likely contributes to the ectopic lipid deposition (i.e.: in non-adipose tissues) and extremely high incidence of coronary artery disease seen in T1DM subjects. Also, due to insulin's potent, fast-acting, glycemia-lowering action, this therapy significantly increases the risk of hypoglycemia; a disabling and life threatening event. Because insulin therapy does not restore metabolic homeostasis, better anti-T1DM intervention is urgently needed. Recent findings in rodents strongly indicate that administration of leptin (a slow-acting, glycemia-lowering hormone) reverses the lethal consequences and many of the metabolic defects caused by insulin deficiency. Because leptin exerts lipolytic action and does not cause hypoglycemia, this hormone represents an attractive alternative and/or adjuvant to current T1DM therapy. Yet, the mechanism underlying leptin's anti-T1DM action is unknown. [(3)]

2.1.2 The Effect of Leptin Hormone Administration in Type 1 Diabetes Mellitus:

Leptin treatment reverses hyperglycemia in animal models of poorly-controlled type 1 diabetes (T1D), spurring great interest in the possibility of treating T1DM patients with leptin.

In mouse models of T1DM, leptin mono-therapy (i.e. without the use of exogenously administered insulin and/or other compounds) corrects the diabetes and lethal catabolic consequences of insulin deficiency. One year of treatment with leptin also remarkably improves glucose and lipid profiles in 2 patients affected by both T1DM and acquired generalized lipodystrophy. Although insulin therapy was not entirely discontinued, leptin treatment improved insulin sensitivity to an extent that insulin doses were significantly reduced (30–50% compared to pre-leptin administration doses) in those subjects. These pre-clinical and clinical findings spurred enthusiasm on the anti-T1DM therapeutic potentials of leptin. As a result, clinical trials aimed at determining the safety of the hormone and its

efficacy to diminishing the insulin requirements, hyperglycemia, glycemic fluctuations, and circulating lipid levels in T1DM humans are ongoing.

2.2 Leptin Treatment in Type 2 Diabetes Mellitus:

2.2.1 Leptin Hormone and Insulin Resistance:

Type 2 Diabetes Mellitus (T2DM) is characterized by insulin resistance, hyperglycemia, and elevated circulating lipid levels; in later stages pancreatic β-cell loss can also occur.

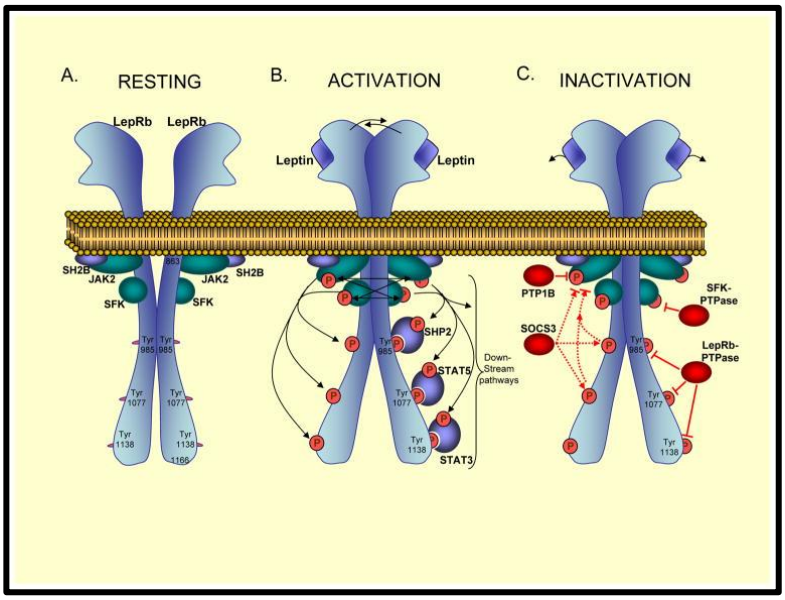
Results from several pre-clinical studies indicate that leptin improves insulin resistance, and glucose and lipid imbalances in mouse models of T2DM. However, the results of two recent clinical trials would indicate that leptin therapy is ineffective (or only marginally effective) in improving diabetes and insulin resistance in obese people affected by T2DM. The anti-T2DM action of leptin may be however unmasked in T2DM patients who are not obese and have normo- or hypo-leptinemia such as for example Asian T2DM populations which in general have low adiposity. Future clinical trials aimed at addressing this possibility are therefore warranted.

Nevertheless, leptin therapy seems not to be effective in people who are leptin resistant. Moving forward, this information would indicate that:

i) a better understanding of the mechanisms underlying leptin resistance is needed,
ii) ways to improve leptin resistance should be looked for, and
iii) research aimed at identifying the molecular mechanisms underpinning the beneficial effects of leptin therapy must be encouraged as results from these endeavours are expected to provide the molecular targets for novel medicines able to circumvent the "leptin resistant" obstacle.

2.2.2 Leptin Hormone as an Anti-Obesity Factor:

The leptin receptor LepRb isoform has a long intracellular domain capable of activating a number of intracellular signaling pathways, including activation of signal transducer and activator of transcription phosphorylation 3 (STAT3). The LepRb-STAT3 pathway is strictly required for the anti-obesity actions of leptin. LepRb is expressed in a relative wide number of hypothalamic and extra-hypothalamic brain regions. Importantly, activation of STAT3 phosphorylation by LepRb is impaired in some, but not all, neuronal groups in the brain of DIO rodents. Specifically, neurons within the ARH exhibit reduced STAT3 activation, while LepRb-expressing neurons elsewhere in the brain appear to have relatively normal leptin sensitivity, indicating that ARH LepRb neurons play a key role in development of leptin-resistant obesity. Not surprisingly, the leptin-resistant ARH neurons in DIO mice include the AgRP- and POMC-expressing neurons which mediate at least part of the anti-obesity effects of leptin [4]



3. Mechanism of Action of Leptin Hormone:

3.1 The Target of Leptin Hormone:

The antidiabetic effect of leptin has been postulated to occur through suppression of glucagon production and/or suppression of glucagon responsiveness; however, there does not appear to be a direct effect of leptin on the pancreatic α-cell. Thus the mechanisms responsible for leptin's anti-diabetic effect remain poorly understood. [(5)]

To search for leptin's targets in the brain, Kong and his team initiated their research based on the often overlooked finding that leptin corrects type 1 diabetes in an insulin-independent manner, thereby successfully bypassing the issue of leptin sensitivity. The Tufts researchers induced diabetes in non-obese adult mice with the drug streptozotocin (STZ), which breaks pancreatic beta cells and stops insulin and leptin production, and then extensively mapped neuronal brain activity.

"We found that AgRP [agouti-related protein-producing] neurons in the hypothalamus were extremely active in these mice, and we suspected that the STZ-induced leptin deficiency was causing this. We were excited when we successfully used leptin to inhibit the AgRP neurons and quickly reverse the diabetes," said the paper's co-first author Christopher Bartolome, a Ph.D. student in the neuroscience program at the Sackler School of Graduate Biomedical Sciences at Tufts where Kong is also a member of the neuroscience and the cell, molecular and developmental biology program faculties.

AgRP neurons had been proposed as a direct target for leptin by early leptin researchers. Subsequently, however, most scientists had discarded that idea because deleting leptin receptors in AgRP neurons using the popular Cre-LoxP gene editing system had failed to replicate either obesity or diabetes found in mice bred to lack leptin receptors. Kong and his team wondered if the chronic obesity and diabetes present in such mice from birth might be obscuring how leptin worked.

To confirm that leptin was indeed targeting AgRP neurons - a finding that flew in the face of prevailing views - the Tufts neuroscientists developed a new CRISPR genome editing technology that used an adeno-associated virus to carry guide RNAs to specifically delete AgRP neuron leptin receptors in young adult mice. The technology's capacity to target adults was important because during development AgRP neurons are known to be susceptible to impacts sometimes associated with Cre-Lox gene editing, a sensitivity that might explain why past studies using Cre-LoxP techniques produced no effects on body weight.

"We found that deletion of leptin receptors in AgRP neurons induced marked obesity and diabetes and largely attenuated leptin's anti-obesity and anti-diabetes effects. This demonstrated that AgRP neurons represent the major site in the brain to mediate leptin's effects," said Kong, who was an early adopter of CRISPR techniques.

3.2 Leptin inhibits AgRP neurons pre- and post-synaptically

The researchers not only identified AgRP as the major neuronal target of leptin in the brain and an important focus for developing obesity and diabetes treatment, but also discovered two distinct mechanisms through which leptin inhibits these neurons: One is a pre-synaptic mechanism in which neurons secreting the powerful neuroinhibitor GABA innervate AgRP

neurons to mediate leptin's acute effects on feeding, and the other is a post-synaptic mechanism in which a potassium channel sensitive to the nucleotide ATP is required for leptin to act on AgRP neurons to regulate energy balance, food intake, and blood sugar.

"These findings are very important because fully understanding the neural basis of leptin's effects could help lead to a better understanding of the causes of obesity, leptin resistance, and, even more importantly, to the development of mechanism-based therapies," said the paper's co-first author Jie Xu, Ph.D., a postdoctoral scholar in the Kong laboratory. **(6)**

Conclusion:

To conclude this review, insulin therapy in the treatment of Diabetes Mellitus has been proved to be beneficial and increases life expectancy, but it has also been proved to have many cardiovascular and other pathological side effects. This has lead scientists to search for new possible treatments and the discovery of Leptin hormone. This hormone is an endogenous satiety hormone that targets the hypothalamus and causes a decrease in appetite. It has also been proved to have some effect on insulin levels. Latest studies have proved that administration of exogenous Leptin hormone can treat both type 1 and type 2 Diabetes Mellitus with much less side effects than insulin therapy.

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