

Relationships between Alteration in Leptin and Glucose Homeostasis

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Abstract

Glucose homeostasis is firmly controlled by insulin and also by leptin adipocytokines. These hormones act significantly on regulating adiposity and food intake in human beings. Leptin effects on the insulin-glucose homeostasis, controlling of body weight (obesity) and adiposity. Leptin secretion and effects are controlled centrally in the hypothalamus and superficially in the muscles, pancreas and liver that regulate the insulin-glucose metabolism via diminishing insulinemia, glycemia, and insulin resistance. Major understanding of the functional effects of leptin on relationship between insulin-glucose homeostasis will enhance the leptin-based targeted therapies against diabetes and other metabolic syndromes (insulin resistance disorders). In study, summarize the regulatory roles between leptin and glucose homeostasis in diabetes.

Keywords: Glucose homeostasis; Insulin resistance; Leptin

Introduction

Leptin belongs to the family of tumor necrosis factor alpha (TNF-alpha), Interleukin-6 (IL-6), leukemia inhibitory factor, granulocyte-colony factor, glycoprotein 130 (gp130) and other cytokine and is therefore considered as cytokine like substance. Leptin, a 16-kDa and 167 amino acid protein secreted from white adipocytes, has been shown to have role in the regulation of food intake, energy expenditure, and whole-body energy balance in rodents and humans [1]. Leptin serum

level correlates with fat stores and reacts according to changes in energy balance [2]. The expression and secretion of leptin is highly correlated with body fat mass and adipocyte size. Cortisol and insulin are potent stimulators of leptin expression, and beta-adrenergic agonists, cAMP, and thiazolidinediones attenuate expression. Leptin is secreted from various sites beside to white adipose tissue, like placental trophoblasts and amnion cells from uteri of pregnant women but the amount of body fat is the main determinant of the circulating levels of this hormone [3].

Role of Leptin in Insulin Secretion

At a peripheral level, Leptin act through the leptin receptors present in the pancreatic islets. Leptin receptor presents in two isoforms, ObRa and ObRb [4,5]. These receptors have significant role in inhibiting secretion of insulin and mainly mediated via three pathways. 1) Inhibition of K-ATP channels by leptin. 2) Leptin inhibits the secretion of insulin through activation of phosphodiesterase 3B (PDE 3B) enzyme. 3) Leptin limits phospholipase C-protein kinase C (PLC-PKC), which increases insulin secretion by inhibiting the ATP-mediated potassium channels via PKA phosphorylation that activates calcium channels [5]. Leptin activates PDE 3B via a PI3K pathway and subsequently diminishes the level of cAMP in beta cells [6]. Reduced level of cAMP is not able to close potassium channels and hence have reduced secretion of insulin. The possible pathways include phosphorylation of signaling proteins such as protein kinase A/C (PKA/C) and calcium/calmodulin-dependent protein kinase (CaMK) pathway.

Correlation between Leptin Expression and Metabolic Status

Leptin has emerged as one of the major signals that relay the status of storage of fat molecules to the hypothalamus and plays a significant role in energy homeostasis process. Leptin acts in the hypothalamus by regulating the intake of food and maintains the body weight by a neural circuitry. It comprises of orexigenic and anorectic signals which includes Neuropeptide Y (NPY), Agouti-Related Protein (AgRP), Melanin Concentrating Hormone (MCH), galanin, Neurotensin (NT), α -Melanocyte Stimulating Hormone (α -MSH), orexin, Cocaine- and Amphetamine-Regulated Transcript (CART) and Corticotropin-Releasing Hormone (CRH). It has been also reported that leptin inhibits the synthesis of all the above-mentioned neuropeptides. In leptin-signaling cascade, the binding of leptin to the receptor results in phosphorylation and activation of Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) pathway [7].

Role of Leptin in Cardiovascular System

Fairly substantial number of studies has shown an association between the concentration of leptin with cardiovascular risk such as, acute myocardial infarction, stroke, coronary heart disease, chronic heart failure and left cardiac hypertrophy [8-12]. The mechanism by which leptin could contribute to these complications remains unknown. The presence of the leptin receptor in the heart suggests that leptin could modulate cardiac function

directly [13]. Few reports have shown a direct effect of leptin on cardiomyocyte contraction that may contribute to altered myocardial function [13,14]. Studies in cardiac cell line demonstrated leptin as the major effector on the adenylate cyclase of beta-adrenergic receptors suggesting its role in the energy metabolism and glucose homeostasis [15].

Conclusion

Leptin and insulin hormones play important roles in energy metabolism, control of food intake and blood glucose homeostasis. Both are directly or indirectly controlled by each other; 1) Insulin triggers leptin secretion and synthesis, 2) Leptin restricts insulin secretion and enhances insulin sensitivity, 3) regulating adiposity, lipotoxicity and insulin-independent action, 4) reduces hepatic production of glucose resulting in glucose-lowering effects, and 5) through osteocalcin, regulating the glucose-insulin homeostasis. The leptin receptor is secreted in various peripheral tissues and, most abundantly, in the brain, which regulates energy homeostasis. It also maintains the activity of the sympathetic nervous system and regulates feeding behaviour in the neuroendocrine pathways.

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