Leptin in Obesity: An Example of altered Homeostasis

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Abstract

The regulation of body weight is a very good example of homeostasis, that it follows the feedback regulatory loops. The adipocyte hormone, leptin (OB protein), is proposed to be an "adiposity signal" that acts in the brain to lower food intake, increase the energy expenditure and thus finally the adiposity. As plasma leptin levels are elevated in most overweight individuals, obesity may be associated with leptin resistance. The saturation capacity of leptin transport to reach its site of action i.e. hypothalamus might be one of the probable mechanism for leptin resistance. This review throws light on the mechanism of genesis of obesity with special interest on the role of leptin and its resistance as an important mechanism.

Key words: Homeostasis, leptin, leptin resistance, obesity

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Introduction

Obesity, which was earlier thought as a disease of affluent society only, now became a pandemic problem, almost equally prevalent in both developed as well as in developing nations. It can be defined as a medical state, in which the surplus body fat got accumulated to such a level that it has an unfavorable effect on health. Various epidemiological studies have shown that obesity increases the chances of different diseases like diabetes mellitus, cardiovascular disorders, obstructive sleep apnea, osteoarthritis etc. which consequently leads to increased total morbidity and mortality[1].

Despite of very well understood ill-effects of obesity, the biological link of genesis of obesity and its complications remains difficult to understand. Obesity is an obvious product of continual positive energy homeostasis. The regulation of calorie intake and expenditure and ultimately metabolic profile that evolve during energy balance are mediated by a complicated network of signals starting from a number of endocrine tissues e.g. pancreas,

adipose tissue, stomach etc. These signals are integrated in the various parts of nervous system involved in the regulation of energy balance.[2]

Leptin: an adipose-derived hormone, an adipocytokine or adipokine

Leptin, the product of the *ob* gene, is a hormone secreted by white adipose tissue. Originally it was proposed to act as an obesity signal, which indicates the copious stores of adipose tissue to the central nervous system (mainly hypothalamus) to control energy intake and augment the energy expenditure. There are a number of evidences involving leptin to the direct regulation of adipose tissue metabolism, via stimulation of lipolysis and inhibition of lipogenesis. Later on, it has been added that the primary role of leptin is in the adjustment to negative energy balance too. Accordingly, reduction in circulating leptin is connected with increased hunger, and leptin substitution prevents the compensatory decline in metabolic rate. [3-5]

Adipose tissues were earlier thought as having only function to store the fat, but now it is widely accepted to have a very dynamic role in energy homeostasis. The terms "adipocytokines" and ''adipokines'' were coined to explain the adipose tissue derived bioactive molecules that have many effects on the normal physiological functions of human beings. Some well known examples of adipokines include Leptin, Adiponectin, Apelin, chemerin, interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), retinol binding protein-4 (RBP4) and tumor necrosis factor-alpha (TNF-α).[6,7] These bio-molecules can be more precisely placed into the larger and constantly increasing list of adipose tissue-derived hormones.

It is highly possible that some of these adipokines may mediate the systemic effects and complications of obesity too. Their relative roles in modifying appetite, energy balance, insulin resistance, their role as immune markers and atherosclerosis are the subjects of intense medical research, as they may prove as modifiable causes of morbidity in obese people.[8]

Genetic causes of human obesity: role of *ob* gene

It is to be expected that the genes implicated in the weight gain increases the vulnerability of a person to the obesity and its complications, when combined with the environmental conditions favoring a positive

energy balance. The genetic mutations causing several familiar pleiotropic obesity syndromes have been recognized, for example, Bardet–Biedl syndrome, Albright's hereditary osteodystrophy syndrome, Cohen syndrome, Alstrom syndrome etc. but, the clear relationship between the products of the mutant genes and abnormal energy homeostasis, has not been well established. The study of strains of genetically obese mice has resulted in the detection of many genes, mutations of which have subsequently been found to lead to severe human obesity.[9, 10]

The deficiency of an *ob gene* product, leptin results in obesity, hyperphagia, infertility, and impaired T-cell–mediated immunity in mice, and the administration of exogenous leptin in them reverse many aspects of the phenotype. Due to deficiency of leptin, *ob/ob* mice develop severe obesity as a result of a combination of increased food intake and diminished energy expenditure. In addition to obesity, the congenital deficiency of leptin in mice results in a wide range of other phenotypic abnormalities.[5, 11, 12] In humans, it was reported first time in two homozygous children to have frameshift mutation in the *ob* gene that resulted in untraceable amount of leptin in their circulation and suffering from a syndrome of hyperphagia and morbid obesity.[13]

Leptin receptors

Leptin can interact with six types of receptors (Ob-Ra to Ob-Rf, or Lep-Ra to Lep-Rf), all of which are encoded by a single gene, LEPR.[14] Ob-Rb is the only receptor isoform that can signal intracellularly via many signal transduction pathways, and is present in hypothalamic nuclei.[5]

Within the hypothalamus, leptin decreases expression of the orexegenic peptides, neuropeptide Y and agouti related peptide, and increases expression of the anorexigenic peptides, POMC and CART, resulting in a decrease in appetite.[15, 16]

Feedback regulation of body weight: an example of normal homeostasis

According to Jéquier E and Tappy L… ''In body weight regulation research, a feedback regulatory loop with three distinct steps has been identified:*1*) a sensor that monitors the level of energy, *2*) hypothalamic centers that receive and integrate through leptin receptors the intensity of the signal, and *3*) effector systems that influence the two

determinants of energy balance, i.e., energy intake and energy expenditure''.[17]

In the regulatory loop of body weight regulation, afferent limb (sensory signal) consists of leptin and other molecules that are secreted in response to adequate fatty stores and constant positive energy balance. The hypothalamus which is the control/ integrator center contains leptin-responsive neurons (or receptors). The binding of leptin to these receptors alters the expression of several genes, which produces specific neuropeptides (orexegenic and anorexegenic both). The efferent limb of the regulatory loop is represented by neuronal network containing neurons with specific receptors for the neuropeptides. These neuropeptides ultimately modulate the food intake and energy expenditure [15, 16, 18]. The autonomic nervous system is also implicated in this efferent limb; leptin increases sympathetic nervous system (SNS) activity which mediates its action on energy expenditure.[19]

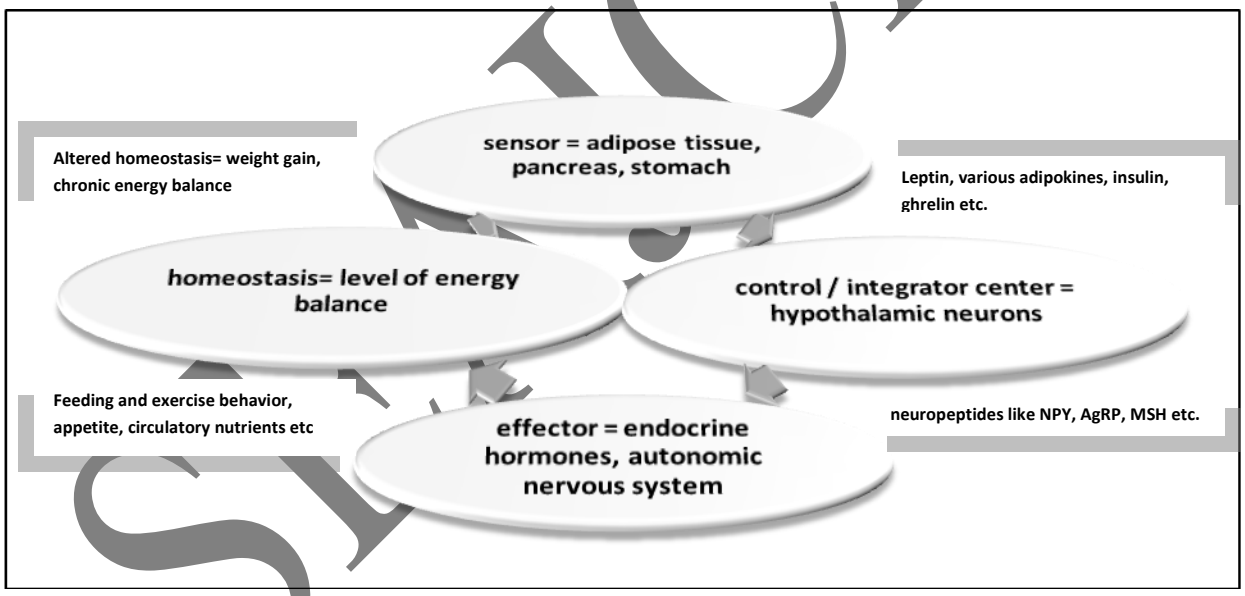

Figure 1: Feedback regulation of body weight: an example of normal homeostasis

Resistance to leptin Action: an example altered homeostasis

In obese individuals, the high plasma leptin levels do not induce the expected responses i.e. the reduction in appetite behavior and an increase in energy expenditure. If these responses were present, we would expect a weight loss and a correction of the obese

state automatically, and then nobody would have been obese. It appears, therefore, that obese humans are resistant to the effects of endogenous leptin.[20]

One mechanism of leptin resistance may be the flaw in the system that facilitates the transport of leptin.[21] Caro et al.[22] showed that leptin leptin enters the brain by a saturable transport system. The capacity of leptin transport was lower in obese individuals, and that may provide for a mechanism for leptin resistance. Schwartz et al.[23] demonstrated that a saturable mechanism mediates CSF leptin transport, and that reduced efficiency of brain leptin delivery among obese individuals with high plasma leptin levels results in apparent leptin resistance. Another implication of this mechanism of leptin resistance is that the use of leptin to treat obesity might be ineffective, if endogenous leptin has already saturated its transporters. The transport system in the brain cells may involve leptin binding sites in the choroid plexus and lepto-meninges.[24-26] Golden et al.[27] demonstrated that a leptin receptor functions at the blood brain barrier (BBB) forming capillary endothelium. Therefore, the BBB leptin receptor could function in similar manner to the leptin receptor at the choroid plexus epithelium. The transport system of leptin through the BBB is also shown to be saturable, by studies of ^{125}I-leptin transport into brain in vivo in the mouse.[21] It has also been suggested that hyperleptinemia might down regulate the leptin transporters in *db/db* mice.[25, 26] Another mechanism possibly lies in the leptin signaling mechanism in leptin-responsive neurons in the hypothalamus.[28]

Recent evidences suggest that leptin resistance associated with obesity may be selective. They were not for all the central as well as peripheral actions of leptin. For example, in agouti obese mice, there is resistance to only the metabolic effects of leptin, but leptin still contributes to the hypertension observed in this model.[29, 30] It has been demonstrated that these mice have preserved renal sympathetic activation despite the loss of the anorectic and weight-reducing effects of leptin.[31, 32] However, the relevance of this mouse model to human obesity is unclear, as no form of human obesity caused by over-expression of agouti or agouti-related proteins has been reported.

Although leptin resistance is sometimes described as a metabolic disorder that

contributes to obesity, similar to the way insulin resistance is sometimes described as a metabolic disorder that has the potential to progress into type 2 diabetes, it is not certain that it is true in most cases. The mere fact that leptin resistance is extremely common in obese individuals suggests it may simply be an adaptation to excess body weight.

Conclusion

The control of energy balance and weight regulation is achieved by several regulatory loops. These networks of regulatory pathways participate in homeostatic responses. The combined responses that control energy intake and expenditure to maintain energy balance have conferred a survival advantage. Leptin is proved as a vital tool to fight against the obesity and to prevent its complications. However, Leptin resistance is posing problems in this field of study; the site, causes and the management methods to overcome leptin resistance is the future research direction.

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