Hypothesis

Is leptin an insulin counter-regulatory hormone?

X. Remesar*, I. Rafecas, J.A. Fernández-López, M. Alemany

Departament de Bioquímica i Biologia Molecular, Facultat de Biologia, Universitat de Barcelona, Av. Diagonal 645, 08028 Barcelona, Spain

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Abstract Leptin, the product of the ob gene, controls appetite through the hypothalamus and may affect many other tissues because of the widespread distribution of its receptors. Leptin is synthesized by white adipose tissue (WAT) under conditions of high energy availability and insulin stimulus. Glucocorticoids enhance this synthesis and catecholamines hamper leptin production. Leptin diminishes insulin secretion by the pancreatic beta cells and induces insulin resistance. In fact leptin hampers insulin action on WAT itself in a negative feedback loop. The evidence acquired in studies on diabetics, starvation, refeeding and insulin and glucose clamps supports this interpretation, which may also explain part of the difficulties encountered by the current postulate that links leptin to WAT mass size signalling to the brain. Leptin may be, essentially, a counter-regulatory hormone limiting the insulin drive to store energy in the form of fat, its effects reaching from a decrease in food intake to lower insulin secretion and increased resistance to insulin and lower glucose uptake and fat synthesis by WAT.

Key words: Leptin; Insulin; Obesity

1. Leptin expression in white adipose tissue

The study of the mechanisms controlling body weight has received an enormous boost during the last year thanks to the identification of the ob gene and its product, leptin, which induces the loss of fat in ob/ob mice [1–3]. Leptin is expressed only in adipose tissues [4], though it is more intensely expressed in white than in brown adipose tissue [5].

The gene db, encoding the leptin receptor has been characterized in mice [6], and in rats, where it has been found to coincide with the fa mutation [7]; its defect results in the overexpression of the ob gene [8]. Leptin down-regulates the expression of the ob gene via paracrine or endocrine pathways, since isolated adipocytes do not respond to direct leptin stimulation [9]. Sympathetic activity or cAMP lowers the expression of the ob gene [9]. In white adipose tissue, β-adrenergic stimulation decreases ob gene expression [5]. Cold exposure, directly related to sympathetic stimulation rewarming, also lowers the synthesis of leptin in adipose tissue, an effect that can be partially reversed by reheating [10].

In vivo leptin release by adipose tissue has been demonstrated in humans and circulating leptin levels are correlated with degree of obesity [11], because of overexpression of the ob gene [12]. Leptin and insulin levels, as well as body weight, are inter-correlated [13]. However, non-insulin-dependent diabetics show leptin levels which do not differ from those of non-diabetic humans of the same body mass index [14].

In normal rats, ob gene expression is down-regulated by insulinemia under euglycemic conditions [15]. The presence of insulin is also required for leptin release [16]. In streptozotocin-diabetic rodents, however, the low levels of ob gene mRNA are not fully restored with continuous insulin treatment in the way that glycemia and other markers are [17]. This has prompted the assumption that the ob gene is not, or is only minimally, regulated by insulin [17]. Obese mice are insensitive to insulin induction of leptin synthesis because of chronic exposure to both glucose and insulin [18]. Leptin secretion also decreases during starvation [19], and increases with refeeding [20].

Hyperinsulinemia induces a rise in adipose tissue ob gene expression in humans [21], but euglycemic hyperinsulinemic and hypoglycemic clamps fail to alter leptin levels [21]. However, euglycemic insulin and hyperglycemic clamps resulted in increased leptin secretion [16]. Short-term insulin administration does not increase leptin secretion in humans [16,21], but insulin affects leptin levels in the long term [16]. The db/db (diabetic) mice, lacking a functional leptin receptor [22], show insulin resistance, overexpression of the ob gene [7], and other pathologies related to diabetes. The Zucker fa/fa rats, also defective in leptin receptors, do not present the modulation of leptin levels induced by starvation, insulin or cold exposure [23].

2. Is leptin a ponderostat signal?

Leptin establishes a link between peripheral tissue-derived information and the central nervous system network [1]. Its main binding site in the brain is the choroid plexus [24]. Systemic leptin lowers the hypothalamic expression of neuropeptide Y in ob/ob mice [26], which have abnormally raised levels of neuropeptide Y mRNA, but has no effect on the db/db mice, lacking functional leptin receptors [26]; overexpression of neuropeptide Y leads to increased appetite, hyperglycemia and obesity [26]. Thus, leptin injected into the hypothalamus inhibits neuropeptide Y synthesis and release [25]. Intracerebroventricular injections of neuropeptide Y induce the expression of the ob gene [27] due to secondary hyperinsulinemia.

The main role attributed to leptin is to act as a ponderostat signal which informs the brain of the mass of fat reserves [28]. However, there are a number of experimental results suggesting that leptin does not fully comply with the requisites of a ponderostat signal as initially postulated [29]. There is a very wide variation in leptin levels in plasma [30], which in addition vary with fasting [19], fat-rich diets [31], carbohydrate ingestion [32] and alterations in blood glucose [18]. All these changes are related to the availability of energy. But leptin is

*Corresponding author. Fax: (34) (3) 4021559.
E-mail: remesar@porthos.bio.ub.es

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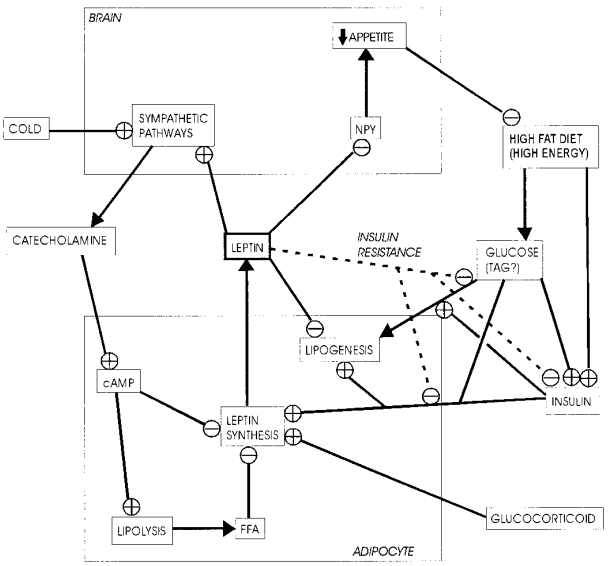

Fig. 1. Modulation of leptin synthesis in adipose tissue by insulin, glycemia, catecholamines and glucocorticoids.

also sensitive to insulin [21], and is affected by glucocorticoids [33] and catecholamines [4] as well as by lipolysis metabolites such as fatty acids [34]. The hormones listed are precisely those which control the fate of the available energy, either by storing fat or by wasting through thermogenesis.

Leptin mRNA levels are unaffected by the size of adipocyte fat stores [34], but leptin production is related to adipose tissue mass [12,30]. Starvation and loss of fat tissue both induce decreases in circulating leptin and adipose tissue ob mRNA levels [18,19], but the post-slimming levels are lower than expected from the remaining body fat. The identification of transport systems helping to cross the blood-brain barrier has increased the possibility that leptin plays a role in the central nervous system [35]. Leptin transport into the CSF is diminished in the obese [36], which provides a basis for human leptin resistance such as that observed in children [37]. However, this transport into CSF is not unique, since it is shared by a number of peptide hormones, in particular insulin, which combine centrally induced effects with peripheral actions on metabolism [38] and a very direct implication on energy partition and the development of obesity.

3. Insulin-leptin interrelationships

The identification of a direct implication of leptin on adipocyte lipid metabolism [39] raises the possibility that leptin may act directly as a hormone on other tissues, i.e. not through the brain-mediated circuits. There is a direct relationship between insulin and leptin, but the latter only responds to the insulin stimulus under conditions of hyperglycemia or high availability of energy [21], since starvation lowers leptin production [19] and normoglycemic hyperinsulinemia fails to raise leptin levels [21]. Carbohydrate feeding increases leptin expression and circulating levels in rats [31]. Leptin is thus secreted when the metabolic signal 'high glucose availability' and the endocrine signal 'insulin' act at the same time, in a coordinated manner, marking a true situation of high lipogenic potentiality. In that case, we postulate that the production of leptin may serve as a signal of a counter-regulatory mechanism preventing the excessive incorporation of reserves into adipocytes (Fig. 1). Hence its effects in diminishing the additional intake of energy and its widely accepted definition as a satiation factor [40], as well as the potentiation of energy expenditure [3], probably mediated through noradrenergic pathways [9]. In addition to these central effects, leptin acts on adipose tissue metabolism, and perhaps on other tissues, since they contain abundant leptin receptors in different structural forms [41]. The consequence of leptin action is the induction of insulin resistance, a diabetogenic trait characterizing db/db mice. In this way leptin tends to diminish the combined effects of insulin and high energy that initially elicited its secretion.

The effects of leptin on other systems and pathways (cytokines, nerve growth factor, etc.), in spite of our sketchy knowledge of them, may give support to a major role for leptin as a counter-regulatory hormone (or paracrine factor acting on adipose tissue itself) which protects adipose tissue (and perhaps other organs and tissues) from excessive lipid synthesis induced by high insulin and ample energy availability.

Leptin receptors have been characterized in β-cells, which allows for negative insulin synthesis feedback [42]. Insulin, in parallel with leptin, is also found in the brain [38] and is also transported by means of a saturable system [43], through the arcuate nucleus [44] acting on the neuropeptide Y levels [44]. Insulin thus exerts central actions which are complementary to the peripheral effects on tissues [38]. Obese humans are often hyperinsulinemic and show resistance to insulin [45] in parallel with raised leptin levels [4,20,30]. The latter decrease when weight is lost or food intake is limited [17,19], situations in which insulin and energy availability (glycemia) are decreased, and as a result insulin resistance decreases. It can be postulated, then, that leptin may be a key factor in the development of insulin resistance in the same way as that found in the db/db mice.

4. Concluding remarks

The changes observed with starvation [19], light cycles [46] and cold exposure [5,10] suggest further modulation by glucocorticoids potentiating leptin production [9,33,34] and catecholamines inhibiting its synthesis through modulation of cAMP levels [9] or lipolysis-derived fatty acids [34]. In any case, this very important role could not coexist nor coincide with the signalling to the brain of body fat mass, and thus we ought to see leptin in the light of a counter-regulatory hormone affecting body weight, not simply as a long-term signal.

Thus, perhaps leptin will not in the end turn out to be the long-sought ponderostat signal. Nevertheless, leptin is a powerful satiation factor and very probably a key insulin counter-regulatory hormone, playing a role – in itself perhaps more important than that of a ponderostat signal – of paramount importance for the understanding of the molecular mechanisms determining not only obesity and energy partition, but also diabetes.

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