Leptin resistance

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Leptin is primarily produced by adipocytes. Its plasma concentration varies in proportion to fat mass. Binding of leptin to its receptors in the hypothalamus and brain stem orchestrates the activity of neuroendocrine ensembles that inhibit food intake and increase energy expenditure. Loss of function mutations of the leptin- or leptin receptor gene are associated with obesity and insulin resistance in rodents. Leptin deficient humans are also morbidly obese, which indicates that leptin plays a critical role in the control of energy balance in man as well as in rodents. Circulating leptin levels are high in most obese humans and apparently do not act to reduce adipose stores to their 'normal' size. Emerging evidence indicates that high fat feeding induces leptin resistance in rodents. Clinical evidence supports the notion that obese humans are leptin resistant as well. Leptin resistance may not only explain the propensity of people to grow obese, it may also underlie various metabolic features of obesity. This paper reviews current perceptions of the causes and consequences of leptin resistance in rodents and man.

Leptin is primarily produced by adipocytes and it acts in the brain to control energy balance and fuel flux via neuronal circuits in hypothalamic and brain stem nuclei. Plasma leptin levels vary in proportion to fat mass in rodents and humans, where large adipose stores are associated with high circulating leptin concentrations. Binding to leptin receptors in the hypothalamus orchestrates the activity of a myriad of neurons that are critically involved in the regulation of food intake and metabolism (1, 2). An increase of the plasma leptin concentration inhibits food intake and stimulates energy expenditure so as to curtail further growth of adipose stores. Conversely, reduction of circulating leptin levels in case of caloric restriction and loss of adipose tissue unleashes appetite and restrains energy expenditure to prevent further weight loss. Genetically engineered, leptin deficient *ob/ob* mice are hyperphagic, insulin resistant and extremely obese (3, 4). They also have low energy expenditure and body temperature. Loss of function mutations of the leptin receptor are asso-

ciated with a similar phenotype in mice and rats (5, 6). In analogy, leptin deficient humans are marked by morbid obesity that manifests in childhood, which illustrates the pivotal role of leptin in the control of energy balance in man (7). However, mutations of the leptin gene are very rare in humans. Indeed, the majority of obese individuals has high circulating leptin levels, as expected in light of their large adipose mass (8, 9). Why do high plasma leptin levels not suppress appetite and increase energy expenditure so as to reduce energy stores to 'normal' in obese humans? Probably because obese humans are leptin resistant. This paper delineates the causes and consequences of leptin resistance in rodents and humans.

Mechanism of action

The leptin receptor (LEPR) is a single membrane spanning receptor that belongs to a family of class I cytokine receptors, including interleukin 6 (IL-6), leukemia inhibitory factor (LIF) and granulocyte-colony stimulating factor (GCSF) (10). Six splice variants ('a' to 'f'), that differ in their intracellular tails, but share identical extracellular binding domains, have been identified to date. Only the 'long isoform', LEPRb, has intracellular motifs necessary for activation of the Janus Kinase (JAK) / Signal Transducer and Activator of Transcription (STAT) signal transduction pathway (11). Binding of leptin to the LEPRb leads to autophosphorylation of JAK 1 and 2 and subsequent recruitment of STAT3. Tyrosine phosphorylated STAT3 transactivates target genes by binding to specific promoter elements (12). Activation of LEPRb also promotes expression of suppressor of cytokine signalling 3 (SOCS-3), which is a negative regulator of leptin signalling and probably serves to switch off or dampen leptin signal transduction (13).

The LEPRb is abundant in various hypothalamic nuclei that are involved in the control of food intake and energy balance, including the arcuate, dorsomedial, ventromedial and lateral nuclei (14). Leptin receptors have also been identified in various other brain areas, including the nucleus of the solitary tract (15) and the caudal brain stem (16, 17). In these nuclei, leptin regulates the transcription and release of a host of distinct neuropeptides that can be categorized as anabolic or catabolic. Anabolic neuropeptides include neuropeptide Y (NPY), Agouti related peptide (AgRP), orexins (ORX) and melanin concentrating hormone (MCH). Genes encoding proopiomelanocortin (POMC), cocaine and amphetamine regulated transcript (CART), and corticotrophin releasing hormone (CRH) are major targets of leptin driving catabolic pathways (18).

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The blood-brain-barrier (BBB) protects the brain against entry of toxins and coordinates the transit of nutrients and hormones from blood to brain (and vice versa). Various periventricular brain areas, including the median eminence and area postrema, lack a functional BBB (19). The arcuate nucleus, a major target of leptin, lies adjacent to the median eminence. This probably allows leptin to access the arcuate freely via diffusion through the median eminence (20). Transit of leptin from blood to other brain areas requires an active and saturable transport process, most likely mediated by short isoforms of the leptin receptor (LEPRa) that are abundant in the chorioid plexus and brain microvasculature (14, 20).

Leptin enters the brain to activate catabolic neural circuits and inhibit anabolic pathways. Thus, when circulating leptin levels are high because fat stores are full, POMC neurons in the arcuate are active and adjacent NPY neurons are silent. These neurons project to the paraventricular nucleus (PVN) and various other hypothalamic nuclei that regulate neuroendocrine ensembles involved in the control of food intake and fuel flux and energy expenditure. In particular, pituitary hormone release and activity of the autonomic nervous system are controlled by hypothalamic leptin signalling (21, 22). Simultaneously, leptin modulates neuronal activity in the brainstem (23). Via these various neuronal circuits, leptin inhibits food intake, increases energy expenditure and reinforces insulin action.

Metabolic and behavioural effects of leptin

Leptin deficient *ob/ob* animals are hyperphagic, insulin resistant and morbidly obese. Their metabolic rate and core body temperature are low. Leptin replacement restores all of these metabolic anomalies (4, 24, 25). Also, *ob/ob* mice are hypotensive despite their obesity (26), and leptin infusion increases arterial blood pressure and heart rate in rats through activation of lumbar and renal sympathetic nerves (27, 28).

A myriad of data indicates that the effects of leptin on food intake and body weight are largely mediated by its impact on arcuate nucleus NPY and POMC neurons. NPY potently stimulates feeding and reduces energy expenditure, whereas α- and β-melanocyte stimulating hormones (α-/β- MSH), split products of the POMC polypeptide precursor, inhibit food intake and increase metabolic rate and blood pressure (18, 29, 30). Leptin suppresses NPY neuronal activity (31, 32), while it promotes POMC expression (33), thereby reducing body weight and increasing arterial pressure. The JAK/STAT cascade alluded to above is responsible for intracellular translation of leptins impact on NPY and POMC gene expression.

Since *in vivo* measures of insulin sensitivity correlate strongly with total and regional fat mass in animals and humans (34), it is tempting to attribute insulin resistance in *ob/ob* mice and leptin deficient humans to their obese phenotype. However, there is evidence to suggest that leptin impacts on glucose metabolism through mechanistic routes that are independent of its

effect on food intake and body weight. Indeed, intraperitoneal administration of leptin acutely reduces glycemia and insulinemia and restores glucose tolerance without affecting body weight in *ob/ob* mice. Injection of a low dose of leptin into the ventromedial hypothalamus of lean rats promotes basal (insulin independent) glucose uptake in various tissues, suggesting that the central nervous system is a critical target of leptin in the control of glucose metabolism (35, 36). The neural routes that mediate leptins effects on food intake and energy expenditure may also modulate insulin action. Indeed, intracerebroventricular (i.c.v.) administration of NPY induces insulin resistance of the liver (37) and activation melanocortin receptors by melanotan II, an analogue of α-MSH, reinforces insulin action in muscle and adipose tissue (38).

Importantly, leptin and POMC appear to have similar and clinically very relevant effects on metabolism in man. Indeed, loss of function mutations of the leptin and POMC genes are associated with hyperphagia, severe obesity and insulin resistance in humans (39, 40). Also, mutations of melanocortin receptors, mediating the effects of α- and β- MSH on body weight, are the commonest form of monogenetic obesity in humans, where mutations leading to complete loss of function are associated with a more severe phenotype (41). Furthermore, leptin reverses insulin resistance in patients with congenital lipodystrophy, a disease that is marked by low circulating leptin concentrations (42-44), indicating that it favourably affects insulin action in humans as well as in rodents.

These data clearly show that leptin has an important role in the regulation of feeding, energy expenditure, body weight and insulin action in rodents and man. However, circulating leptin levels are increased, and apparently fail to curtail the growth of adipose stores in obese humans (8, 9). How can this be explained? Emerging evidence indicates that high fat feeding induces leptin resistance in rodents and clinical data suggest that obese humans are also leptin resistant.

Leptin resistance

High fat fed murine models of obesity are widely accepted models of common human obesity, because high fat feeding in rodents recapitulates the metabolic and endocrine features of obesity in man. The circulating leptin concentration is high in diet induced obese (DIO) rats and mice (8, 45). Apparently, leptin does not curtail the progression of obesity in these animals, which suggests that it has less biological effect on food intake and metabolism. At least 3 mechanisms may be responsible for leptin resistance:

1. impaired transit of leptin across the BBB;
2. reduced number of leptin receptors in critical target sites, or
3. post-receptor signal transduction defects.

Initial experiments revealed that high fat feeding almost completely blocks the ability of plasma leptin to activate STAT-3 in hypothalamic nuclei (46). Accordingly, the hypophagic response to peripheral leptin administration is blunted in high fat fed mice (47). Subsequent studies show that leptin transport

across the BBB is reduced in high fat fed rats, although the mechanism remains unclear because LEPRa gene expression is normal in cerebral microvessels (48, 49). There is evidence to suggest that triglycerides may somehow be involved (50). Notably, caloric restriction restores leptin transit across the BBB to normal in DIO, indicating that the defect is reversible (48).

The hypophagic response to i.c.v. leptin administration in rats is also clearly blunted in DIO rats (51), which indicates that high fat feeding impairs leptin signal transduction at the level of the receptor or beyond. Indeed, the LEPRb receptor number is reduced in the hypothalamus of rats that are prone to grow obese on a high fat diet even before they gain weight (52). Moreover, *ex vivo* binding of leptin is clearly impaired in the hypothalamus of DIO rats (53), and the number of LEPRb receptors is also reduced in the hypothalamus of DIO mice (54). Caloric restriction reverses deficits of LEPRb gene expression and protein in DIO rats (55). Other studies reveal that leptin resistance of aging is also associated with reduced hypothalamic LEPRb protein (56). These data strongly suggest that LEPRb number is reduced in high fat fed leptin resistant animals and that the defect can be restored by caloric restriction.

There is also data to indicate that high fat feeding compromises post-receptor cascades involved in leptin signal transduction. SOCS-3, which is induced by activation of the LEPRb, blocks leptin-induced tyrosine phosphorylation of JAK2 (57), and thereby partakes in an intracellular negative feedback loop to curtail leptin signal transduction (13). Neural cell-specific deletion of SOCS-3 enhances hypothalamic STAT-3 phosphorylation in response to LEPRb activation. Moreover, neuron-specific SOCS-3 deficient mice are resistant to high fat diet induced obesity, and leptin inhibits feeding to a greater extent in these animals (58). Conversely, in high fat fed rodents, SOCS-3 expression is significantly increased, and leptin-induced STAT-3 phosphorylation is completely blocked in the arcuate nucleus of the hypothalamus, but not in other brain areas (59). The pathogenic mechanism explaining this phenomenon remains to be determined. However, *region specific* up-regulation of SOCS-3 expression in the arcuate nucleus most likely contributes to leptin resistance in high fat fed rodents.

Interestingly, selective leptin resistance may explain the development of hypertension in response to high fat feeding. Leptin elevates blood pressure by activating sympathetic outflow to the kidneys (60). Leptins capacity to stimulate renal sympathetic nerve activity and elevate blood pressure is fully preserved in high fat fed rats, despite pronounced leptin resistance of feeding and body weight responses (61). This is probably because leptins impact on sympathetic outflow to the kidney is mediated by the dorsomedial (DMH) and ventromedial hypothalamus (VMH) (62), whereas it effects on energy balance are primarily orchestrated by arcuate neurons. As noted above, high fat feeding up-regulates SOCS-3 in the arcuate, but not in other brain areas, including the DMH and VMH (59). Thus, hyperleptinemia, induced by leptin resistance of arcuate neurons and consequent gain of adipose mass, unabatedly stimulates renal sympathetic outflow to increase blood pressure in diet induced obese rats (61).

What is the evidence to support the presence of leptin resistance in obese humans? First of all, hyperleptinemia apparently does not curtail adipose tissue growth in the majority of obese individuals (8, 9). Secondly, exogenous leptin administration has virtually no effect on body weight in obese humans (63, 64). Thirdly, the cerebrospinal fluid / serum leptin concentration ratio is decreased in human obesity, suggesting that leptin transit across the BBB is impaired in obese individuals (65). Finally, the fact that renal norepinephrine spillover (a proximate measure of sympathetic outflow) is increased in obese humans, whereas measures of sympathetic activity in other tissues are reduced (66), is consistent with the presence of regional leptin resistance.

Clinical implications

As a direct corollary of leptin resistance, NPY expression is increased and POMC expression is reduced in the arcuate nucleus of obese, high fat fed animals (67-69). Obviously, these neuropeptides are responsible for the behavioural and metabolic ramifications of leptin resistance. This notion opens new alleys for the treatment of obesity. Indeed, NPY receptor antagonists (70) and melanocortin receptor agonists (71) are currently scrutinized for their potential as weight reducing and insulin sensitizing agents. Other possibilities include the use of peptides other
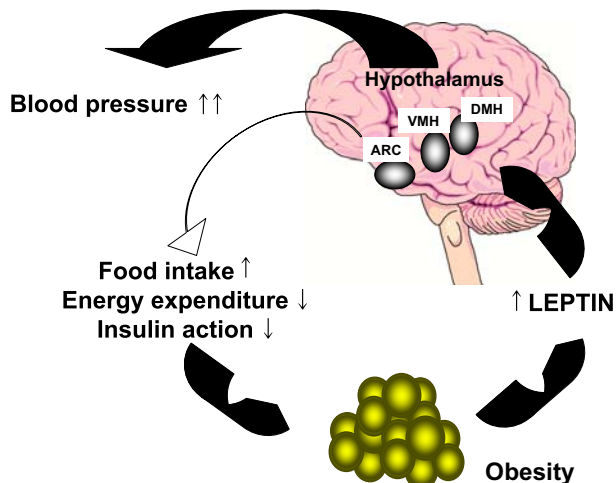

Figure 1. The concept of selective leptin resistance. High fat feeding leads to site specific disruption of leptin signal transduction cascades in the arcuate nucleus of the hypothalamus (ARC). Therefore, leptin does not properly inhibit food intake and fails to increase energy expenditure. Moreover, leptin resistance in the arcuate hampers systemic insulin action. Adipose stores grow and produce more leptin. Leptin signal transduction in the ventromedial (VMH) and dorsomedial (DMH) nuclei of the hypothalamus remains unabated. Through these nuclei, leptin activates renal sympathetic outflow and elevates blood pressure. Thus, selective leptin resistance can explain many of the metabolic features of human obesity.

than leptin that favourably modify NPY and POMC expression levels (72, 73) or drugs that redirect post-receptor leptin signal transduction (74).

Conclusion

Leptin plays an important role in the control of energy balance and insulin action in humans, as evidenced by the fact that leptin deficiency leads to morbid obesity and insulin resistance in childhood. Accordingly, leptin acts in the brain to inhibit food intake, increase energy expenditure and reinforce insulin action. Leptin deficiency is a very rare condition in humans. In contrast, many obese humans have a high circulating leptin concentration, which apparently does not prevent the growth of their adipose tissue, suggesting that leptin action is impaired. High fat feeding in rodents, which recapitulates many of the metabolic features of human obesity, unequivocally leads to (site specific) leptin resistance. Various clues suggest that obese humans are also leptin resistant. Clarification of the downstream neuroendocrine corollaries of leptin resistance may guide the development of novel strategies for the treatment of obesity.

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Samenvatting

Leptineresistentie. Pijl H. Ned Tijdschr Klin Chem Labgeneesk 2007; 32: 3-8.

Leptine wordt voornamelijk door adipocyten gemaakt. De plasmaconcentratie van leptine stijgt met toenemen van de vetmassa. Binding van leptine aan receptoren in de hypothalamus en hersenstam coördineert de activiteit van neuronale circuits die de voedselinname remmen en het energieverbruik stimuleren. Leptinedeficiëntie en inactiverende mutaties van de leptinereceptor leiden tot ernstig overgewicht en insulineresistentie bij knaagdieren. Leptinedeficiënte mensen zijn ook morbide adipeus, hetgeen aangeeft dat leptine bij mensen, net als bij knaagdieren, een buitengewoon belangrijke rol speelt in de regulatie van de energiebalans. De plasmaleptineconcentratie is hoog bij de meeste adipeuze patiënten. Kennelijk beïnvloeden die hoge concentraties de energiebalans niet zodanig dat de vetreserve wordt teruggebracht tot 'normaal'. Er is veel bewijs dat hoogvette voeding leidt tot leptine resistentie bij knaagdieren. Er zijn ook aanwijzingen dat adipeuze mensen leptineresistent zijn. Leptineresistentie kan niet alleen de ongeremde groei van vetreserves verklaren, het zou ook ten grondslag kunnen liggen aan een aantal metabole afwijkingen die met adipositas zijn geassocieerd. Dit overzichtsartikel beschrijft de huidige inzichten in de pathogenese en gevolgen van leptinedeficiëntie in knaagdieren en mensen.

Trefwoorden: leptine; adipocyten; insulineresistentie; obesitas

Adiponectin, role in insulin resistance, atherosclerosis and carcinogenesis

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Adiponectin is one of the many adipokines secreted by adipocytes. Several isoforms are detectable in the circulation, the HMW isoform is supposed to be the most active one. Two adiponectin receptors have been cloned: Adipo R_1 and Adipo R_2 with a different distribution pattern. Stimulation of these receptors is followed by activation of intracellular signaling molecules like AMP kinase and PPARα. Plasma adiponectin levels are lower in obesity and in men compared to women and are influenced by weight reduction, dietary intake and drugs.

Adiponectin might be the important signal protein from the adipocyte to the vascular wall in the pathogenesis of atherosclerosis. Adiponectin inhibits several processes, which play a role in atherogenesis like smooth muscle cell proliferation and foam cell formation. Adiponectin is positively related to HDL levels. Adiponectin is inversely related to several obesity-associated cancers. Adiponectin inhibits carcinogenesis directly via stimulation of apoptosis and indirectly via inhibition of growth factors like insulin and ILGF-1 and the inhibition of angiogenesis. Adiponectin has anti-diabetic properties. It decreases hepatic glucose output and increases muscular fatty acid oxidation and glucose uptake. Measuring plasma adiponectin levels may be worthwhile in the future for detecting subjects with an increased risk for the development of cancer, atherosclerosis and type 2 diabetes. Mechanisms to increase plasma levels of adiponectin and its action via Adipo R_1 and Adipo R_2 may lead to new therapeutic interventions.

Keywords: adiponectin; adiponectin receptor; obesity; atherogenesis; cancer; diabetes

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Adipose tissue can be considered as an organ with various functions (1). In the last decennium it became evident that the adipocyte is secreting several different proteins, also referred to as adipokines (figure 1), that play an important role in cardiovascular integrity, metabolism, inflammation and the development of cancer. From epidemiological and clinical studies it has become clear that obesity is related to cardiovascular disease, disturbances in carbohydrate and lipid metabolism and several different forms of cancer. This relation is especially true between these diseases and the amount of visceral fat. Visceral fat cells are metabolically the most productive ones, compared with