Leptin, Neuropeptide Y and Obesity

LEPTİN, NÖROPEPTİD Y VE ŞİŞMANLIK

Gönen DENİZ*, Şahan SAYGI**

* Ass.Prof.Dr., GATA, Department of Pharmacology,
**Ass.Prof.Dr., GATA, Department of Analytical Toxicology, Ankara, TURKEY

Summary

Obesity is a highly prevalent disorder that is associated with high mortality rate from related diseases such as cardiovascular and metabolic diseases. It is caused by an imbalance between energy intake and energy expenditure, which is influenced with both environmental and genetic factors.

The discovery of leptin has led to better understanding of the obesity. Leptin is a peripheral hormone produced by the adipocytes and is thought to play a key role in the regulation of energy balance. Leptin, the product of the obese gene, inhibits food intake, stimulates energy expenditure and reduces body weight possibly suppressing hypothalamic neuropeptide Y activity. Obesity in ob/ob mice is caused by a mutation in the ob gene resulting in a lack of functional leptin.

Leptin acts as a satiety factor by binding to receptors in the hypothalamus and the plasma levels of leptin are highly correlated with body fatty mass. Its expression increases after food intake and decreases during fasting and diabetes.

This review briefly summarizes the role of leptin and neuropeptide Y in the regulation of food intake and body weight.

Key Words: Leptin, NeuropeptideY, Obesity

T Klin J Med Sci 2002, 22:217-220

Özet

Kardiyovasküler ve metabolik hastalıklara yol açan ve yüksek ölüm oranı taşıyan şişmanlık oldukça yaygın bir rahatsızlıktır. Enerji alımı ile enerji harcanması arasındaki dengesizliğe bağlı olarak gelişen şişmanlık hem çevresel hem de genetik faktörlerin etkisi altındadır.

Leptinin keşfi şişmanlığın daha iyi anlaşılabilmesine yol açmıştır. Leptin yağ hücrelerinde üretilen ve enerji dengesinin düzenlenmesinde anahtar rolü oynadığı düşünülen bir periferik hormondur. Leptin bir obez gen ürünü olup muhtemelen hipotalamik bir hormon olan nöropeptid Y'i baskılamak suretiyle besin alımını inhibe eder, enerji harcanmasını stimüle eder ve vücut ağırlığını azaltır. Genetik olarak şişman farelerde şişmanlık, obez gende bir mutasyona bağlı leptin fonksiyonunda oluşan bir eksiklik sonucu meydana gelmektedir.

Leptin hipotalamustaki reseptörlere bağlanarak bir doygunluk faktörü gibi hareket eder ve plazma seviyeleri vücut yağ kitlesi ile yüksek korelasyon gösterir. Leptin ekspresyonu besin alımı ile artar, açlık ve diyabette azalır.

Bu derlemede leptin ve nöropeptid Y'nin besin alımı ve vücut ağırlığının regülasyonundaki rolünü özetledik.

Anahtar Kelimeler: Leptin, Nöropeptid Y, Şişmanlık

T Klin Tıp Bilimleri 2002, 22:217-220

Obesity

Obesity is a common medical condition most often due to an imbalance between energy intake and expenditure (1). It is a major risk factor for morbidity and mortality from a variety of diseases including hyperlipidemia, hyperglycemia and hypertension. Studies indicated that obesity is the result of genetic, environmental and neuroendocrine factors. The regulation of weight and weight gain is a complex process that involves a number of behavioral, social and hormonal factors (2-4).

The process of the weight gain in obesity is more complex. The discovery of both leptin and Neuropeptide Y (NPY) has led to a better understanding of the pathophysiology of obesity (5-7). Several anatomic regions play a central role in regulating fat stores. The hypothalamus is indeed known to modulate food intake and energy partitioning. The mammalian hypothalamus strongly influences ingestive behavior through several different signaling molecules such as leptin, NPY and insulin (2). Damage to the ventromedial nucleus (VMN) or the paraventricular nucleus (PVN) in the hypothalamus produces massive obesity in mammals and birds. Injury to the central nucleus of amygdala will also produce obesity in contrast to the lateral hypothalamus (8).

The identification and sequencing of the mouse obese (ob) gene in 1994 opened important new avenues in obesity research (9,10). Leptin, the obese gene product, is produced by adipocytes and is secreted in plasma and acts particularly within the hypothalamus (11,12). It inhibits

food intake, stimulates energy expenditure and reduce body weight. NPY, the hypothalamic neurotransmitter is a potent stimulant of appetite and feeding which also reduce energy expenditure (13,14,15). The expression and release of hypothalamic NPY are inhibited by leptin (16). The interaction between leptin and NPY concentration has been considered an important factor in the regulation of body weight (17). Obese individuals have hyperleptinemia (18). It is believed that obesity is the result of resistance to leptin. The increase in plasma leptin levels observed with increasing adiposity, such as that obese humans may be resistant to the putative effects of leptin (19).

Obesity is a chronic medical condition that may require long term treatment, therefore the risks and benefits of all pharmacological agents must be carefully considered (1). The treatment of obesity requires modulation of both energy intake and energy expenditure, and pharmaceutical treatments are being developed to complement the traditional means of dietary restriction and exercise (20).

Obesity has now become a major target for drug development not only for affecting obesity but also for managing and preventing some conditions, such as diabetes and cardiovascular diseases (4).

Leptin

The discovery of a "fat melting hormone" named leptin (Greek root, leptos meaning thin) by Friedman JM raised the hopes in human obesity (21). In 1958, Hervey GR first demonstrated the presence of a hormone that regulated body weight through an interaction with the hypothalamus (22). The cloning and characterization of the ob gene had showed that it encodes a hormone, leptin, that is expressed in adipose tissue and lower levels in gastric epithelium and placenta (3,23). Identification of the obese (ob) gene and its protein product, leptin has increased understanding of the pathophysiology of obesity (6,20,24).

Leptin is synthesized in the adipocytes, circulates in the blood, binds the proteins, and acts on central neural networks especially in hypothalamus. It inhibits food intake, stimulates energy expenditure, and reduces body weight (14,16,25,26), and is postulated to act as a satiety factor by binding to receptors in the hypothalamus (27).

The first step to understand leptin action has been taken when Tartaglia, et al discovered the leptin receptor (Ob-R) (28). The effects of leptin suggest regulation at the level of the hypothalamus. Leptin receptors have been localized to the choroid plexus and hypothalamus. It was first isolated from mouse choroid plexus by expression cloning and identified as a member of the cytokine family of receptors. There are two major isoforms of the leptin receptors. First isoform, short leptin receptor (Ob-Ra) is believed to function as a transporter and it seems to be responsible for transporting leptin across the blood-brain barrier in the hypothalamus, this receptor is defective in obese diabetic db/db mice. Second isoform, long leptin receptor (Ob-Rb) is believed to function as the first leptin signaling step (3,14,29). Leptin receptors are expressed at different levels in different tissues of mice, mainly in the brain, heart, testes, and adipose tissues.

Leptin appears to play a major role in the control of body fat stores through coordinated regulation of feeding behavior, metabolism, energy balance, and autonomic nervous system in rodents, primates, and humans. It provides a communication link between fat tissue and brain, that is thought to be blood borne signal from the adipose tissue that informs the brain about the size of the body fat mass (19,30). There is a strong positive correlation between serum levels of leptin and adipose tissue mass. Leptin levels increase with increasing body fat. Therefore, serum leptin levels reflect the amount of adipose tissue in the body in humans and animals. Serum levels of leptin in normal weight subjects are in the 5 ng/ml range and reach 50 ng/ml in obese subjects. Weight gain leads to higher blood levels and weight loss to lower levels (5,31-33).

Leptin expression increases after food intake, and decreases during fasting and diabetes. Daily administration of recombinant leptin produces striking weight loss in the ob/ob mice. Furthermore, weight loss after leptin administration in animals is not only due to decreased appetite and food consumption, but also increase in thermogenesis and activity level (3,10,16,19).

The raised leptin levels in obese people have been interpreted as a consequence of relative insensitivity to endogenous leptin, possibly caused by deficient functioning of leptin receptors in the brain (29).

The aberrant secretion of leptin and deficient leptin receptor function have all been shown to cause obesity in animal models and humans. Leptin deficiency and/or receptor defects and resistance to leptin perception by specific brain centers, and reduced efficiency of leptin uptake into the hypothalamus have been proposed as possible mechanisms for unrestricted weight gain (2,31).

Leptin is an increasingly convincing candidate in the central regulation of energy homeostasis. However, many peripheral and central factors play a role on the effects of leptin such as insulin, NPY, glucocorticoids, melanocyte stimulating hormone, and galanin. Leptin is thought to influence energy homeostasis mainly by regulating the expression of hypothalamic neuropeptides, which then influence feeding behavior, autonomic and neuroendocrine function.

NPY is a critical component of the biological response to leptin levels. For example, levels of orexigenic peptide NPY are increased in the hypothalamus as a result

of leptin deficiency and starvation, and this over expression is decreased by leptin administration. This interaction may be important in regulating energy balance and body fat mass (16,34,35). Anabolic peptides are inhibited by leptin and catabolic peptides are stimulated by leptin. One of the leptin's main effects may be to inhibit synthesis and release of hypothalamic NPY. It is hypothalamic neurotransmitter and potent stimulant of appetite and feeding which increases food intake and body weight (13,14,15,36). NPY is now recognized as an important endogenous appetite transducer. NPY producing neurons that participate in the daily management of feeding behavior are localized in the arcuate nucleus of the hypothalamus in the brain-stem (7). Levels of NPY are increased in the hypothalamus as a result of leptin deficiency in ob/ob mice (16,27,37,38). Chronic administration of NPY into the hypothalamus of normal animals mimics the phenotype of leptin deficiency including obesity and reduced thermogenesis. NPY deficiency does also partially ameliorate the obesity and all of the adverse endocrine effects of leptin deficiency in ob/ob mice, so NPY antagonists and leptin are of interest as potential anti obesity agents (4).

Leptin has been reported to normalize hyperglycemia and hyperinsulinemia in ob/ob mice (39,40). Experimental data suggest that insulin is an important regulator of leptin expression in adipose tissue. Moreover, leptin may have direct effect on insulin action (32,41). In ob/ob mice exogenous leptin lowers plasma insulin levels. Leptin circulates at concentrations proportionate to both body adiposity and plasma insulin levels. Recent studies showed such as a complex relationship between leptin and insulin or insulin resistance and obesity (6,17,23). The interaction between insulin insensitivity and leptin concentration may be important in the regulation of body weight. It has been hypothesized that insulin resistance itself protects against weight gain. Glucocorticoids have also an inhibitory effect on the action of leptin (42).

Anorexia nervosa patients have extremely low leptin levels. Re-feeding of these patients results in a rapid increase in plasma leptin concentration to roughly normal levels before normal weight is achieved. That is excessive leptin production plays a permissive role in the pathogenesis of this condition (3).

The mechanism by which centrally administrated leptin leads to lipolysis and the loss of adipose tissue mass is unknown. The metabolic response to leptin is markedly different from the response to reduced food intake. Whereas dieting leads to the loss of lean body mass and adipose tissue mass, leptin induces weight loss in specific for the adipose tissue mass.

The possible therapeutic benefit of leptin treatment in humans is now being studied in clinical trials. Studies show that four weeks of daily leptin injection (0.3 mg/kg) are safe and cause small but significant weight loss in lean and obese subjects. The ability to optimize the pharmacokinetics of recombinant leptin may greatly influence its usefulness. Administration of leptin by injection or with greater potency as a constant subcutaneous infusion results in a dose dependent decrease in body weight at incremental increases of plasma leptin levels within the physiological range. For example, leptin is more potent when administered as a subcutaneous infusion, whereas once-daily intraperitoneal injection is largely ineffective (33). The manipulation of leptin and NPY are under investigation for the treatment of obesity.

Leptin Resistance

In general, obese animals have higher leptin levels than controls, indicating that this form of animal obesity is associated with leptin resistance (3,15). The concentration of leptin in the peripheral circulation is about four fold higher in obese individuals compared with the lean. Thus, since the expected response to hyperleptinemia is decreased caloric intake and increased energy expenditure, most obese humans are probably insensitive to endogenous leptin production. In lean subjects with relatively low adipose tissue, the majority of circulating leptin is in the bound form. In obese individuals, the majority of leptin circulates in free form which is the bioactive protein, and thus obese subjects are resistant to free leptin (27).

The role of leptin in the pathogenesis of obesity may be the result of resistance of leptin. The basis for leptin resistance in obese hyperleptinemic human subjects is clearly unknown. The great majority of obese subjects don't have a defect in the production of leptin. Leptin resistance can be due to a defect in transporter system (blood-brain barrier and blood-cerebrospinal barrier). Leptin transport may be normal but defect may lie in the leptin receptor. It is possible that both leptin transport and its receptor are normal and the defect lies in the signaling mechanism. Leptin resistance makes exogenous leptin less suitable as a treatment for obesity in humans.

The pathogenesis of most human obesity is unknown and likely to be result of disturbances in leptin secretion or leptin sensitivity. The relative importance of leptin, NPY and other peripheral signals of fat mass require further investigation.

REFERENCES

1. Carek PJ, Dickerson IM. Current concepts in the pharmacological management of obesity. Drugs 1999; 57(6): 883-904.
2. Richard L, Bradley C, Bentley C. Regulation of ob gene expression and leptin secretion by insulin and dexamethasone in rat adipocytes. Diabetes 1999; 48: 272-8.
3. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature 1998; 395: 763-70.

4. Hirschberg AI. Hormonal regulation of appetite and food intake. Ann Med 1998; 30(1): 7-20.
5. McNeely JM, Boyko JE, et al. Association between baseline plasma leptin levels and subsequent development of diabetes in Japanese Americans. Diabetes Care 1999; 22: 65-70.
6. Ruige BJ, Decker MJ, et al. Leptin and variables of body adiposity, energy balance, and insulin resistance in a population based study. Diabetes Care 1999; 22: 1097-104.
7. Yokosuka M, Kalra SP, and Kalra PS. Inhibition of NPY induced feeding and c-fos response in magnocellular paraventricular nucleus by a NPY receptor antagonist: A site of NPY action. Endocrinology 1999; 140: 4494-500.
8. Rray GA, York DA. The MONA LİSA hypothesis in the time of leptin. Recent Prog Horm Res 1998; 53: 95-117.
9. Schwartz WM, Prigeon LR, et al. Evidence that plasma leptin and insulin levels are associated with body adiposity via different mechanisms. Diabetes Care 1997; 20(9): 1476-81.
10. Hamann A, Matthaai S. Regulation of energy balance by leptin. Exp Clin Endocrinol Diabetes 1996; 104(4): 293-300.
11. Bado A, Levasseur S, et al. The stomach is a source of leptin. Nature 1998; 394: 790-3.
12. Mistry AM, Swick AG, Romsos DR. Leptin rapidly lowers food intake and elevates metabolic rates in lean and ob/ob mice. J Nutr 1997; 127(10): 2065-72.
13. Baskin DG, Breininger FJ, Schwartz MW. Leptin receptor mRNA identifies a subpopulation of NPY neurons activated by fasting in the hypothalamus. Diabetes 1999; 48: 828-33.
14. Houseknecht KI, Raile CA, Matteri RI, Spurlock MF. The biology of leptin.J Anim Sci 1999; 76(5): 1405-20.
15. Palmiter RD, Frickson JC, Hollopeter G, Raraban SC, Schwartz MW. Life without NPY. Recent Prog Horm Res 1998; 53: 163-99.
16. Ahima SR, Kelly J, Elmquist KJ, and Flier SJ. Distinct physiologic and neuronal responses to decreased leptin and mild hyperleptinemia. Endocrinology 1999; 140: 4923-31.
17. Segal KR, Landt M, and Klein S. Relationship between insulin sensitivity and plasma leptin concentration in lean and obese men. Diabetes 1996; 45: 988-91.
18. Chen MD, Song YM, Lin PY. Zinc may be a mediator of leptin production in humans. Life Science 2000; 66(22): 2143-9.
19. Caro FJ, Sinha KM, et al. Leptin: The tale of an obesity gene. Diabetes 1996; 45: 1455-62.
20. Strader CD, Macintyre DF, Candelore MR, Parker FM. Molecular approaches to the discovery of new treatments for obesity. Curr Opin Chem Biol 1997; 1(2): 204-9.
21. Zhang Y, Friedman J, et al. Positional cloning of the mouse obese gene and its human homologue. Nature 1994; 372: 425-32.
22. Harvey GR. The effects of lesions in the hypothalamus in parabiotic rats. J Physiol 1958; 145: 336-52.
23. Mathiak K, Gowing J, et al. Serum leptin levels, body fat deposition, and weight in females with anorexia or blumia nervosa. Horm Metab Res 1999; 31: 274-7.
24. Aubert MI, Pierroz DD, et al. Metabolic control of sexual function and growth role of NPY and leptin. Mol Cell Endocrinol 1998; 140: 107-13.
25. Kalra PS, Dube MG, Farmerie WG, and Kalra SP. Evidence that dark phase hyperphagic induced by neurotoxin 6 hydroxydopamine may be due to decreased leptin and increased NPY signalling. Physiol Rehav 1998; 63(5): 829-35.
26. Sahu A. Leptin decreases food intake induced by melanin concentrating hormone, galanin and NPY in the rat. Endocrinology 1998; 139(11): 4739-42.
27. Nedvidkova J. Leptin. Cesk Fysiol 1997; 46(4): 182-8.
28. Tartaglia LA, Dembski M, et al. Identification and expression cloning of leptin receptor OB-R. Cell 1995; 83: 1263-76.
29. Hotani S, Bjorbaek C, et al. Functional properties of leptin receptor isoforms. Diabetes 1999; 48: 279-86.
30. Donahue CP, Prineas R, et al. Is fasting leptin associated with insulin resistance among nondiabetic individuals? Diabetes Care 1999; 22: 1092-6.
31. Güven S, Bershawi AE, et al. Plasma leptin and insulin levels in weight reduced obese women with normal body mass index. Diabetes 1999; 48: 347-52.
32. Persson B, Westergren M, Celsi G, Nord E, and Ortgvist E. Leptin concentrations in cord blood in normal newborn infants and offspring of diabetic mothers. Horm Metab Res 1999; 31: 467-71.
33. Morin H, Parlemuter I. Leptin: A genetic solution to obesity. Presse Med 1997; 26(16): 770-3.
34. Flier JS. What's in a name? In search of leptin's physiologic role. J Clin Endocrinol Metab 1998; 83: 1407-13.
35. Schwartz MW, Seeley RS, Campfield LA, Burn P, Baskin DG. Identification of targets of leptin action in rat hypothalamus. J Clin Invest 1996; 98: 1101-6.
36. Dreyden S, Brown M, King P, William G. Decreased plasma leptin levels in lean and obese zucker rats after treatment with serotonin. Horm Metab Res 1999; 31: 363-6.
37. Wang Q, Bing C, Barazanji AK, et al. Interactions between leptin and hypothalamic NPY neurons in the control of food intake and energy homeostasis in the rat. Diabetes 1997; 46: 335-41.
38. Vuagnat RA, Pierroz DD, Euglaro P, et al. Evidence for a leptin-neuropeptide Y axis for the regulation of growth hormone secretion in the rat. Neuroendocrinology 1998; 67(5): 291-300.
39. Wang JL, Chinookoswong N, Scully S, et al. Differential effects of leptin in regulation of tissue glucose utilization in vivo. Endocrinology 1999; 140: 2117-24.
40. Pelleymounter MA, Cullen MS, Baker MB, et al. Effects of the obese gene product on body weight regulation in ob/ob mice. Science 1995; 269: 540-3.
41. Ookuma M, Ookuma K, York AD. Effects of leptin on insulin secretion from isolated pancreatic islets. Diabetes 1998; 47: 219-23.
42. Zakrzewska KE, Cusin I, Sainsbury F, et al. Glucocorticoids as counterregulatory hormones of leptin. Diabetes 1997; 46: 717-9.

Geliş Tarihi: 12.04.2001

Yazışma Adresi: Dr.Gönen DENİZ
GATA Tıbbi Farmakoloji AD Başkanlığı
06018, Etlik, ANKARA