Leptin: The New & The Old (Minireview)

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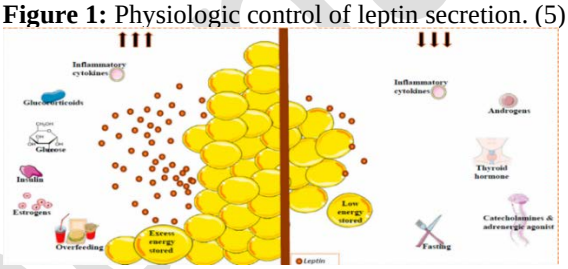
Leptin is produced by white adipose tissue. The main central effects are appetite suppression and increased energy consumption. Leptin synthesis is reduced by weight loss, leading to increased energy uptake and reduction in consumption. Leptin has other beneficial effects related to puberty and immunity. Obesity is associated with increased circulatory leptin levels, which is not able to suppress appetite (leptin resistance). However, this resistance is selective, as hyperleptinemia in obesity is associated with harmful effects (insulin resistance, increased sympathetic activity, hypertension, endothelial dysfunction, inflammation, and platelet activation). Hyperleptinemia has been reported as a risk factor for coronary artery disease.

Leptin therapy is indicated in rare genetic leptin deficiency, lipodystrophy, and anorexia nervosa. Recently, drugs as GLP-1 analogues, oxytocin, uroguanylin (duodenal peptide) and meta-chlorophenylpiperazine (an agonist for both 5-HT2C and 5-HT1B receptors) have been used to reduce leptin resistance.

Leptin is a hormone secreted from white adipose tissue (adipokine). It was discovered in mice by Jeffrey Friedman group in 1994. (1) The nomenclature originated from the Greek word leptós- λεπτός which means thin. Leptin levels are directly proportional to body fat stores. (2) A direct relation is observed between serum leption and BMI. (3) The main physiologic action was considered to decrease appetite and stimulate thermogenesis by inhibiting the orexigenic neurons (neuropeptide Y) and increasing the anorexigenic neurons (cocaine amphetamine related transcript – CART, and proopiomelanocortin) in the hypothalamus. (4)
Unfortunately, serum leptin levels are increased in obesity, with failure to influence appetite control and weight loss. The term leptin resistance was coined, and was postulated to occur at a central level (hypothalamic leptin receptors). (5)
When fat is lost, leptin levels decrease. This stimulates hunger and inhibits satiety, with reduction in resting metabolic rate. This is actually the real and main physiologic effect.

Control of Leptin Secretion:
A Circadian rhythm exits with highest levels in evening and early morning. It is stimulated by glucocortcoids, glucose, insulin, estrogens and overfeeding. It is inhibited by androgens, thyroid hormones, catecholamines and fasting. (5) (Figure 1)
Mean serum leptin is much lower in normal Egyptian men in comparison to women (0.7 ng/ml versus 17.9 ng/ml) (6)

Figure 1: Physiologic control of leptin secretion. (5)



Leptin effects:
Beneficial:

a- Decreased appetite and increase in energy expenditure. (4)
b- Metabolism: (differentiation of preadipocytes to adipocytes, stimulation of lipolysis, conversion of white adipose tissue to brown adipose tissue, control of insulin resistance. In overweight individuals, leptin levels are high, and an increase in preadipocyte number to facilitate the expansion of fat depots could be expected to avoid fat accumulation in other tissues. (2,3,5) Figure 2.
c- Immunity: Immune system competence, stimulation of macrophage adhesion, phagocytosis, and proliferation of T cells (7)
d- Puberty: Leptin has been considered important for puberty induction. A positive correlation was observed between serum leptin and FSH levels during GnRH testing (6)

Harmful (8):

a- Increased sympathetic activity.
b- Hypertension.
c- Endothelial dysfunction.
d- Inflammation.
e- Platelet activation.

Leptin and cardiovascular disease (CVD)

Circulating leptin is considered a risk factor for CVD. (9) A meta-analysis of different prospective studies confirmed hyperleptinemia as an important risk for coronary heart disease (CHD). (10) In a British study, in 550 men with fatal coronary CHD or nonfatal myocardial infarction and in 1,184 controls nested within a prospective setting, a moderate association was observed between serum leptin and CHD that was largely dependent on BMI. (10) A direct correlation was reported between serum leptin and carotid intima media thickness in patients with type 2 diabetes mellitus. (11) Moreover, high circulating levels were reported in patients with dilated cardiomyopathy (12). A comprehensive review of the harmful effects of leptin on the cardiovascular system was published by Katsiki et al. (8) Figure 3.

Figure 2: Metabolic effects of Leptin (5)

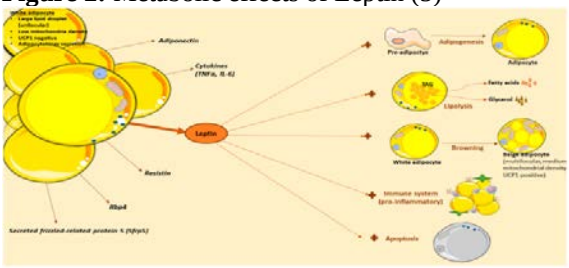
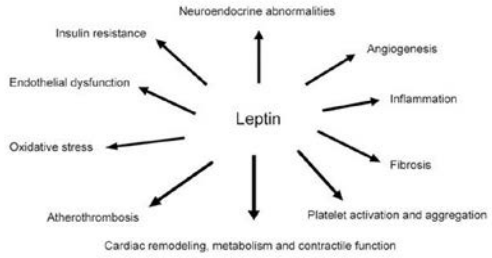


Figure 3: Effects of leptin on the cardiovascular system. (8)



Hyperleptinemia has been involved in the pathogenesis of obesity induced hypertension. In a group of obese Egyptian individuals, serum leptin correlated with mean systemic arterial blood pressure. (3) Selective leptin resistance was observed with preserved agonist effect on the sympathetic nervous system, despite loss of the good metabolic effects of leptin. This can promote for hypertension. (13) Apart from the central effect of leptin to increase vascular tone, a peripheral effect do exist (reduction of nitric oxide, increase in endothelin 1). (14)

Leptin in clinical practice:

The original hope of using leptin to treat obesity actually vanished by the presence of leptin resistance in obese individuals.

Metreleptin (Leptin analog) subcutaneous daily injection has been approved since 2014. (15)

Leptin therapy is useful in rare genetic cases of leptin deficiency. These cases are associated by obesity, insulin resistance/diabetes mellitus (DM), hyperphagia, and high tissue fat/lipotoxicity. (16)

Generalized lipodystrophy is a rare disease characterized by the absence of fat cells, leptin and adiponection secretion. Its clinical features include severe insulin resistance/DM, dyslipidemia (VLDL), fatty liver and pancreatitis. They are corrected with leptin injection. Chronic leptin treatment improves insulin-stimulated hepatic and peripheral glucose metabolism in severely insulin-resistant lipodystrophic patients. Improvement in insulin action leads to reduction in hepatic and muscle triglycerides. Leptin therapy could reverse severe hepatic and muscle insulin resistance and associated hepatic steatosis in patients with lipodystrophy. (17)
Other recent uses of leptin include anorexia nervosa and hypothalamic amenorrhea. (4)

Drugs that increase sensitivity of leptin receptors (agonists) may treat obesity. Chronic oxytocin administration has been advocated as a treatment against impaired leptin signaling or leptin resistance in obesity. (18,19) GLP-1 analogs have been reported to improve leptin resistance. (20) GLP-1 receptor agonist administration may inhibit weight loss-induced increases in soluble leptin receptors thereby preserving free leptin levels and preventing weight regain after weight loss programs or batiatric surgery. (21) Other molecules as uroguanylin (duodenal peptide), meta-chlorophenylpiperazine (an agonist for both 5-HT2C and 5-HT1B receptors), and amylin/ pramlintide decreases have been reported to improve leptin resistance. (22,23) The effects of leptin sensitizers on CVD need to be studied further.

Conclusion:

Obesity is associated with leptin resistance, which makes leptin not useful as a treatment for simple obesity. Selective leptin resistance is associated with harmful cardiovascular consequences. Recent drugs that reduce leptin resistance might be useful tools for the treatment of obesity and cardiovascular protection.

References:

1- Zhang Y, Proenca R, Maffei M, et al. Barone M, Leopold L, Friedman JM. Postional cloning of the mouse obese gene and its human homologue. Nature 1994, 372: 425-32.

2- Liuzzi A, Savia G, Tagliaferri M, Lucantoni R, Berselli ME, Petroni ML, De Medici C, Viberti GC. Serum leptin concentration in moderate and severe obesity: relationship with clinical, anthropemetric and metabolic factors. Int J Obes Relat Metab Disord 1999; 23: 1066-73.

3- Abbassy A.A., El-Din A.G., Cunningham G.R., Atta M.N., Assaad S.N., Rizk M.M., Eid W.E. Study of serum leptin and other hormones in android obesity: relation to hypertension and insulin resistance. The Endocrine Society's 85th Annual Meeting, June 2003, Philadelphia, USA.

4- Seoane-Collazo P, Martínez-Sánchez N , Edward Milbank E , Cristina Contreras C. Incendiary Leptin. Nutrients 2020 Feb 13;12(2):472.

5- Martinez-Sanchez N. There and back again: leptin actions in white adipose tissue. Int J Mol Sci 2020; 21: 6039.

6- Abbassy A.A., Kamel S.S., Assaad S.N., Marzouk S.A., Awad A.B. The relation of leptin and neuropeptide-Y to the hypothalamic pituitary gonadal axis in patients with hypogonadism. The Endocrine Society's 84th Annual Meeting, June 2002, San Francisco, USA.

7- Abella A, Scotece M, Conde J, Pino J, Gonzalez-Gay MA, Gómez-Reino JJ, Mera A, Lago F, Gómez R, Gualillo O. Leptin in the interplay of inflammation, metabolism and immune system disorders. Nature Reviews Rheumatology 2017;13: 100–9.

8- Katsiki N , Dimitri P Mikhailidis DP , Banach M. Leptin, cardiovascular diseases and type 2 diabetes mellitus. Acta Pharmacol Sin 2018 ; 39: 1176-1188.

9- Zeng R, Xu C-H, Xu Y-N, Wang Y-L, Wang M. Association of leptin levels with pathogenetic risk of coronary heart disease and stroke: a meta-analysis. Arq Bras Endocrinol Metabol 2014; 58: 817-23.

10- Sattar N , Wannamethee G, Sarwar N, Chernova J, Lawlor DA, Kelly A, Wallace AM, Danesh J, Whincup PH. Leptin and coronary heart disease: prospective study and systematic review. J Am Coll Cardiol 2009 ; 53: 167-75.

11- Yamazaki Y, Emoto M, Morioka T, Kawano N, Lee E, Urata H, TsuchikurSa S, Motoyama K, Mori K, FukumotoS, Shoji T, Nishizawa Y, Inaba M. Clinical impact of the leptin to soluble leptin receptor ratio on subclinical carotid atherosclerosis in patients with type 2 diabetes. J Atheroscler Thromb 2013; 20: 186-94.

12- Bobbert P, Jenke A, Bobbert T, Kühl U, Rauch U, Lassner D, Scheibenbogen C, Poller W, Schultheiss H-P, Skurk C. High leptin and resistin expression in chronic heart failure: adverse outcome in patients with dilated and inflammatory cardiomyopathy. Eur J Heart Fail 2012; 14: 1265-75.

13- Rahmouni K. Differential Control of the Sympathetic Nervous System by Leptin: Implications for Obesity. Clin Exp Pharmacol Physiol Suppl. 2007 Nov 1; 34 Suppl(s1): S8–S10

14- Rahmouni K, Morgan DA, Morgan GM, Mark AL, Haynes WG. Role of selective leptin resistance in diet-induced obesity hypertension. Diabetes 2005, 54: 2012-18.

15- Chou K, Perry CM. Metreleptin: first global approval. Drugs. 2013 Jun;73(9):989-97.

16- Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ, Sewter CP, Digby JE, Mohammed SN, Hurst JA, Cheetham CH, Earley AR, Barnett AH, Prins JB, O'Rahilly S. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 1997 Jun 26;387(6636):903-8.

17- Brown RJ, Araujo-Vilar D, Cheung PT,Dunger D, Garg A, Jack M, Mungai L, Oral EA, Patni N, Rother KI, von Schnurbein J, Sorkina E, Stanley T, Vigouroux C, Wabitsch M, Williams R, Yorifuji T. The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline. J Clin Endocrinol Metab 2016 ;101: 4500-11

18- Altirriba J, Poher A-L, Rohner-Jeanrenaud F. Chronic Oxytocin Administration as a Treatment Against Impaired Leptin Signaling or Leptin Resistance in Obesity. Front Endocrinol (Lausanne). 2015 ; 6: 119.

19- Spetter MS, Hallschmid M. Current findings on the role of oxytocin in the regulation of food intake. Physiol Behav 2017 ; 176: 31-9

20- Clemmensen C, Chabenne J, Finan B, Sullivan L, Fischer K, Kuchler D, Sehrer L, Ograjsek T, Hofmann SM, Schriever SC, Pfluger PT, Pinkstaff J, Tschöp MH, Dimarchi R, Müller TD. GLP-1/glucagon coagonism restores leptin responsiveness in obese mice chronically maintained on an obesogenic diet. Diabetes 2014; 63: 1422–1427.

21- Iepsen EW, Lundgren J, Dirksen C, Jensen J-EB, Pedersen O, Hansen T, Madsbad S, Holst JJ, Torekov SS. Treatment with a GLP-1 receptor agonist diminishes the decrease in free plasma leptin during maintenance of weight loss. Int J Obes (Lond) 2015; 39, 834–41.

22- Yan C, Yang Y, Saito K, Xu P, Wang C, Hinton Jr AO, Yan X, Wu Q, Tong Q, Elmquist JK, Fukuda M, Yong Xu Y. Meta-chlorophenylpiperazine enhances leptin

sensitivity in diet-induced obese mice. Br J Pharmacol 2015 ; 172: 3510-21.

23- Folgueira C, Daniel Beiroa D, González-Rellán MJ, Porteiro B, Milbank E, Castelao C, García-Palacios M, Casanueva FF, López M, Diéguez C, Seoane LM, Nogueiras R. Uroguanylin Improves Leptin Responsiveness in Diet-Induced Obese Mice. Nutrients 2019; 11: 752.

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