Pathogenesis of obesity

Josanne Vassallo MD, MSc, PhD, FRCP, FACP, FACE

Associate Professor, Department of Medicine, Faculty of Medicine and Surgery
University of Malta Medical School, Guardamangia, Malta
Email: josanne.vassallo@um.edu.mt

The escalating prevalence of obesity worldwide is an ever increasing source of concern to disease surveillance units, health monitoring agencies and healthcare providers globally. Resource allocation in healthcare has had to be tailored to the management of this global epidemic. However the key to success in tackling this problem lies in prevention and this in itself mandates a thorough understanding of the physiology of weight control and the pathogenesis of obesity. The development of obesity is undoubtedly multifactorial with the major underlying causes being inappropriate diet and lifestyle. Genetic factors have been shown to modulate the phenotypic expression of obesity. Medications such as steroids and endocrine disorders such as hypothyroidism can also lead to disturbances in the normal physiology of weight control in a small percentage of instances. However in the vast majority of weight problems and obesity, the aetiology is a mismatch between food intake and energy expenditure.

The physiological basis of obesity

A complex feedback control system consisting of a central processing unit which receives afferent signals and generates appropriate efferent stimuli in response controls food intake, satiety and subsequently weight.

Age and gender differences in food intake have been identified with an increase in adolescence, peaking in the second decade after which it declines.[1] Men tend to eat more than women in keeping with their higher fat free mass.[2] An age-related decrease in food intake is associated with a slow decline in energy expenditure and in middle age the latter is faster than the former. Concomitantly the decline in sex steroid levels occurring in the perimenopause results in an increase in visceral fat and an increased risk of the development of the metabolic syndrome (Figure 1). The latter is a constellation of manifestations originally described by Gerald Reaven in 1993 comprising obesity, insulin resistance and increased atherosclerotic risk with diabetes, hypertension and hyperlipidaemia.[3]

The regulatory control system

The feedback system regulating body weight and appetite is the target of ongoing intense research with appreciation of the complexity of this system increasing as new modulators and players are identified.

Afferent signals

Gastric distension via activation of vagal afferents is a signal for satiety, with gastric contractions signalling for hunger. Nutrients, neural impulses and hormones themselves act as afferent signals in the regulation of energy intake and expenditure (Figure 2). Nutrient absorption eg that of glucose[4] initiates a sensation of satiety whereas a fall in glucose promotes hunger. This effect is itself mediated by different neurotransmitters, hormones and peptides

Leptin[5] is a peptide produced by adipocytes which has been closely correlated with fat mass, with secretion increasing as fat deposition increases. It acts to reduce food intake and is believed to increase sympathetic nervous system activity.[6] This peptide has found use in a small number of individuals who have been shown to be deficient in the leptin gene.

Another important peptide is Growth Hormone (GH) relin which is secreted by the stomach and duodenum and has been shown to stimulate GH secretion. It is an endogenous ligand for the GH receptor. GH relin increases food intake and its secretion is in turn suppressed by food intake.[7-9] Serum concentrations increase in anticipation of a meal. Its secretion has been shown to increase after diet- and exercise-induced weight loss and is believed to be one of the reasons why lifestyle modification does not lead to permanent weight loss.
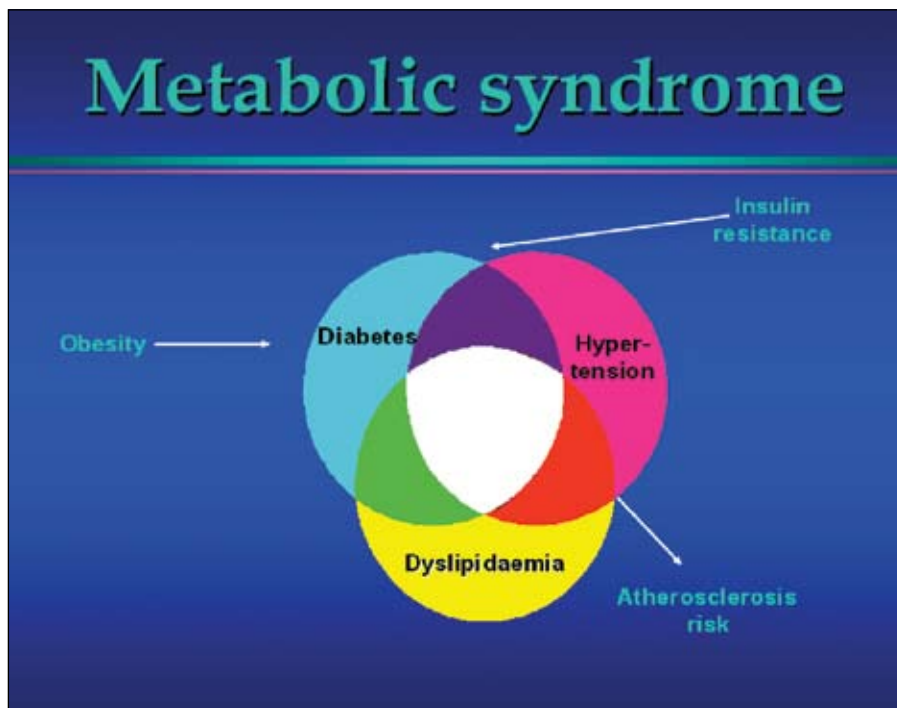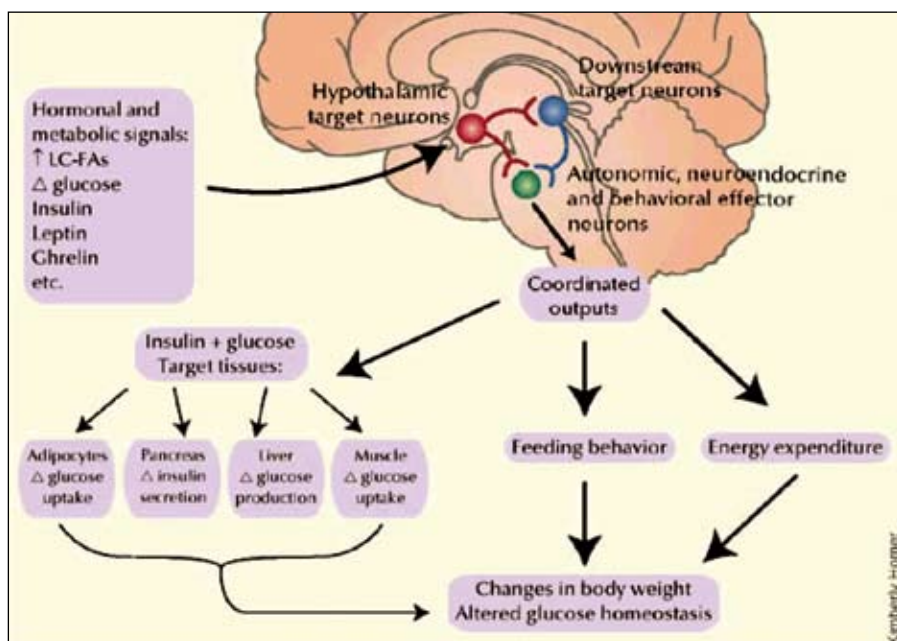
Figure 1: Features of the metabolic syndrome

Figure 2: Overview of the integrated regulatory pathway

Table 1: Monoamines and peptides that affect feeding	
Stimulatory	*Inhibitory*
GH releasing hormone	Leptin
Neuropeptide Y	Cholecystokinin
Melanin-concentrating hormone	Enterostatin
Opioids	Serotonin
Norepinephrine	CRH/urocortin
	Alpha melanocyte stimulating hormone
	Glucagon-like peptide 1

Other peptides that have been shown to reduce food intake are cholecystokinin (CCK), [10] enterostatin[11] and polypeptide Y 3-36.[12] The list of peptides is ever on the increase but the precise interaction between them and their relevance in humans awaits the outcome of further research (Table 1).

Central processing unit

Afferent impulses proceed centrally to the hindbrain and the hypothalamus for integration and processing. A number of specific anatomical sites have been implicated as a result of *in vivo* studies generally involving destruction of the said area and observation of outcomes.[13] The nucleus of the tractus solitarius in the hindbrain is the site where vagal and other neural input are integrated.

The arcuate nuceus at the base of the hypothalamus receives signals from leptin and in turn increases both production and secretion of neuropeptide Y (NPY) and Agouti-related peptide(AgRP) thereby increasing food intake. On the other hand, cocaine-amphetamine-related transcript (CART) and pro-opiomelanocortin (POMC) decrease food intake.

The paraventricular nucleus of the hypothalamus is itself stimulated by peptides from arcuate nucleus and relays signals further. Destruction of the ventromedial hypothalamus has been show to lead to increased food intake and subsequently obesity in animals treated experimentally. The lateral hypothalamic nucleus in turn exerts opposite effects such as decreased feeding and lowering body weight. Furthermore specific areas of the amygdale can affect feeding partially through the ventromedial hypothalamus.

Efferent mediators

The peripheral nervous system has a definite role in stimulating thermogenic tissues via activation of beta 3 adrenergic receptors resulting in a reduction in food intake.[14] The sympathetic nervous system plays a tonic role in maintaining energy expenditure. Amongst the hormones that interact at the efferent end of the regulatory system, glucocorticoids are believed to play an important permissive role[15] these effects possibly mediated via the sympathetic nervous system. For

example, it has been noted that leptin deficiency does not result in obesity in the absence of glucocorticoids.

Factors affecting energy expenditure

Seventy percent of daily energy expenditure in man is utilised in maintaining basal metabolic processes whereas ten percent is utilised in the thermic response to food. An inter-individual variation has been noticed in humans which is believed to be multifactorial:

a) A strong relationship between total daily expenditure or resting energy expenditure and fat free mass is present. Therefore it is believed that differences in fat free mass account for approximately 80% of variance.[16]

b) The sedentary lifestyle prevalent in the Western world definitely contributes significantly to the ever increasing prevalence of obesity.[17,18]

c) Activity and exercise including spontaneous physical activity such as fidgeting can account for one to eight hundred kcal energy expenditure per day.[16, 19]

Genetics of obesity

Obesity can be either monogeneic or polygenic in inheritance. Five single gene defects have been identified:

a) **Agouti gene:** The protein binds to melanocortin-4 receptor in the hypothalamus thereby modulating food intake. Concentrations have been found to be higher in obese than non-obese men and correlate well with basal metabolic index (BMI).[20] A related gene which has been identified is the mahogany gene.[21]

b) **Leptin gene:** Leptin is produced in fat cells, the gut, and the placenta and signals the brain about the amount of stored fat.[22,23] Deficient mice have hyperphagia, insulin resistance and

infertility. In humans leptin may act on the arcuate nucleus to decrease NPY production (which usually stimulates food intake). Obesity due to leptin deficiency has been reported in two families, affected subjects responding well to leptin therapy.[24,25] In contrast the majority of obese subjects have a high level of circulating leptin level suggesting a level of leptin resistance.[26]

c) **Leptin receptor gene:** Leptin receptor deficiency secondary to mutations in the leptin receptor gene has been reported in humans.[27]

d) **Melanocortin-4[28] and melanocortin-3 receptor gene defects[29]:** Transgenic mice with mutations in these genes exhibit hyperphagia and severe obesity. Observations in these mice suggest that receptors for MSH normally inhibit food intake and fat accumulation.

e) **Serotonin** subtype receptor elimination in transgenic mice results in similar manifestations.[30]

Genetic factors

The heritability of weight, metabolic rate, thermic responses to food and spontaneous physical activity has been studied in families which included twins or adoptees. Twins separated at birth maintained the same characteristics regarding weight control despite different environmental backgrounds. Similarly studies in adopted children showed that regulation of weight and body composition

was similar to that of biological parents and differered from that of the adoptive parents.[31,32]

A number of genetic syndromes featuring obesity have also been described in the literature and are associated with chromosomal aberrations as in the Prader Willi Labhart syndrome.[33]

Studies to identify genetic abnormalities in common obesity have so far proved unsuccessful, not an common situtation in polygenic disorders.[34] A number of candidate genes have been analysed such as the beta3 receptor gene,[35] peroxisome proliferators-activated-receptor (PPAR) gamma[36], and melanocortin-4 (MCR-4) receptor.[37,38]

Conclusion

Obesity is a multifactorial and complex disorder that has significant implications for affected subjects and the healthcare services that have to deal with the consequences of this disorder. For example, a recently identified genetic polymorphism[39] in 10% of 4 study populations in the United States (rs7566605 on chromosome 2q14.1) can be expected to have a significant impact on health and healthcare despite being associated with only a low relative risk. Further research into the physiology and pathophysiology of obesity should hopefully enable the development of preventive and therapeutic strategies to curb the obesity epidemic.

References

1. Bray, GA. Contemporary diagnosis and management of obesity. Handbooks in Health Care Co, Newtown, PA 1998.

2. Kromhout, D. Changes in energy and macronutrients in 871 middle-aged men during 10 years of follow-up (the Zutphen Study). Am J Clin Nutr 1983; 37:287.

3. Reaven, GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988; 37:1595.

4. Campfield, LA, Brandon P, Smith FJ. On-line continuous measurement of blood glucose and meal pattern in free-feeding rats; the role of glucose in meal initiation. Brain Res Bull 1985; 14:605.

5. Considine, RV, Sinha, MK, Heiman, ML, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996; 344:292.

6. Bray, GA, York, DA. Leptin and clinical medicine: a new piece in the puzzle of obesity. J Clin Endocrinol Metab 1997; 82:2771.

7. Cummings, DE, Weigle, DS, Frayo, RS, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med 2002; 346:1623.

8. Wren, AM, Seal, LJ, Cohen, MA, et al. Ghrelin enhances appetite and increases food intake in humans. J Clin Endocrinol Metab 2001; 86:5992.

9. Druce, MR, Wren, AM, Park, AJ, et al. Ghrelin increases food intake in obese as well as lean subjects. Int J Obes Relat Metab Disord 2005; 29:1130.

10. Barrachina, MD, Martinez, V, Wang, L, et al. Synergistic interaction between leptin and cholecystokinin to reduce short-term food intake in lean mice. Proc Natl Acad Sci U S A 1997; 94:10455.

11. Erlanson-Albertsson, C, York, D. Enterostatin a peptide regulating fat intake. Obes Res 1997; 5:360.

12. Batterham, RL, Cohen, MA, Ellis, SM, et al. Inhibition of food intake in obese subjects by peptide YY3-36. N Engl J Med 2003; 349:941.

13. Berthoud, HR. Multiple neural systems controlling food intake and body weight. Neurosci Biobehav Rev 2002; 26:393.

14. Grujic, D, Susulic, VS, Harper, ME, et al. Beta-3-adrenergic receptors on white and brown adipocytes mediate beta-3-selective agonist-induced effects on energy expenditure, insulin secretion, and food intake. J Biol Chem 1997; 272:17686.

15. Tataranni, PA, Young, JB, Bogardus, C, Ravussin, E. A low sympathoadrenal activity is associated with body weight gain and development of central adiposity in Pima Indian men. Obes Res 1997; 5:341.

16. Ravussin, E, Lillioja, S, Anderson, TE, et al. Determinants of 24-hour energy expenditure in man: methods and results using a respiratory chamber. J Clin Invest 1986; 78:1568.

17. Robinson, TN. Reducing children's television viewing to prevent obesity: a randomized controlled trial. JAMA 1999; 282:1561.

18. Levine, JA, Schleusner, SJ, Jensen, MD. Energy expenditure of nonexercise activity. Am J Clin Nutr 2000; 72:1451.

19. Bogardus, C, Lillioja, S, Ravussin, E, et al. Familial dependence of the resting metabolic rate. N Engl J Med 1986; 315:96.

20. Katsuki, A, Sumida, Y, Gabazza, EC, et al. Plasma levels of agouti-related protein are increased in obese men. J Clin Endocrinol Metab 2001; 86:1921.

21. Nagle, DL, McGrail, SH, Vitale, J, et al. The mahogany protein is a receptor involved in suppression of obesity. Nature 1999; 398:148.

22. Zhang, YY, Proenca, R, Maffei, M, et al. Positional cloning of the mouse obese gene and its human homolog. Nature 1994; 372:425.

23. Campfield, LA, Smith, FJ, Burn, P. The OB protein (leptin) pathway a link between adipose tissue mass and central neural networks. Horm Metab Res 1996; 28:619.

24. Montague, CT, Farooqi, IS, Whitehead, JP, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 1997; 387:903.

25. Farooqi, IS, Jebb, SA, Langmack, G, et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med 1999; 341:879.

26. Considine, RV, Considine, EL, Williams, CJ, et al. Evidence against either a premature stop codon or the absence of obese gene mRNA in human obesity. J Clin Invest 1995; 95:2986.

27. Clement, K, Vaisse, C, Lahlou, N, et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 1998; 392:398.

28. Huszar, D, Lynch, CA, Fairchild-Huntress, V, et al. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. Cell 1997; 88:131.

29. Chen, AS, Marsh, DJ, Trumbauer, ME, et al. Inactivation of the mouse melanocortin-3 receptor results in increased fat mass and reduced lean body mass. Nat Genet 2000; 26:97.

30. Lucas, JJ, Yamamoto, A, Scearce-Levie, K, et al. Absence of fenfluramine-induced anorexia and reduced c-fos induction in the hypothalamus and central amygdaloid complex of serotonin 1B receptor knock-out mice. J Neurosci 1998; 18:5537.

31. Stunkard, AJ, Harris, JR, Pedersen, NL, McLearn, GE. The body-mass index of twins who have been reared apart. N Engl J Med 1990; 322:1483.

32. Stunkard, AJ, Sorensen, TI, Hanis, C, et al. An adoption study of human obesity. N Engl J Med 1986; 314:193.

33. Ohta, T, Gray, TA, Rogan, PK, et al. Imprinting-mutation mechanisms in Prader-Willi syndrome. Am J Hum Genet 1999; 64:397.

34. Rankinen, T, Perusse, L, Weisnagel, SJ, et al. The human obesity gene map: the 2001 update. Obes Res 2002; 10:196.

35. Lonnqvist, F, Thome, A, Nilsell K, et al. A pathogenic role of visceral fat beta 3-adrenoceptors in obesity. J Clin Invest 1995; 95:1109.

36. Valve, R, Sivenius, K, Miettinen, R, et al. Two polymorphisms in the peroxisome proliferator-activated receptor- gamma gene are associated with severe overweight among obese women. J Clin Endocrinol Metab 1999; 84:3708.

37. Farooqi, IS, Keogh, JM, Yeo, GS. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. N Engl J Med 2003; 348:1185.

38. Lubrano-Berthelier, C, Le Stunff, C, Bougneres, P, Vaisse, C. A homozygous null mutation delineates the role of the melanocortin-4 receptor in humans. J Clin Endocrinol Metab 2004; 89:2028.

39. Herbert, A, Gerry, NP, McQueen, MB, et al. A common genetic variant is associated with adult and childhood obesity. Science 2006; 312:279.