Pathogenesis of obesity

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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. Men tend to eat more than women in keeping with their higher fat free mass. 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.

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 glucose4 initiates a sensation of satiety whereas a fall in glucose promotes hunger. This effect is itself mediated by different neurotransmitters, hormones and peptides.

Leptin5 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. 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. 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.
Other peptides that have been shown to reduce food intake are cholecystokinin (CCK), enterostatin and polypeptide Y 3-36. 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. The nucleus of the tractus solitarius in the hindbrain is the site where vagal and other neural input are integrated.

The arcuate nucleus 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. 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; these effects possibly mediated via the sympathetic nervous system. For

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### Table 1: Monoamines and peptides that affect feeding

<table>
<thead>
<tr>
<th>Stimulatory</th>
<th>Inhibitory</th>
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<tbody>
<tr>
<td>GH releasing hormone</td>
<td>Leptin</td>
</tr>
<tr>
<td>Neuropeptide Y</td>
<td>Cholecystokinin</td>
</tr>
<tr>
<td>Melanin-concentrating hormone</td>
<td>Enterostatin</td>
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<tr>
<td>Opioids</td>
<td>Serotonin</td>
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<tr>
<td>Norepinephrine</td>
<td>CRH/urocortin</td>
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<td></td>
<td>Alpha melanocyte stimulating hormone</td>
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<td>Glucagon-like peptide 1</td>
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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 interindividual 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. 14

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 monogenic 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). 7,10 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. 20,22 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 receptor gene defects: 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. 29

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 differed 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 situation in polygenic disorders. 16 A number of candidate genes have been analysed such as the beta3 receptor gene, 30 peroxisome proliferators-activated-receptor (PPAR) gamma, 31 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 19 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.

Practice Points

1. Obesity has reached epidemic proportions worldwide
2. The pathogenesis of obesity is multifactorial with genetic and environmental/lifestyle mediators playing a role
3. A complex regulatory system exists comprised of a central processing unit which analyses and responds to afferent input and sends out efferent messages
4. A number of genetic mutations predisposing to obesity have been identified in animals and humans
5. The major cause of obesity is energy intake/output mismatch
References


