Pathophysiology and aetiology of obesity

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Abstract

Obesity develops when cumulative energy intake exceeds energy expenditure. The biological processes regulating energy balance are highly regulated. However, these mechanisms can easily be overwhelmed by a willingness to eat when not hungry if attractive food is provided in inductive settings and if individuals are habitually sedentary for long periods. Control pathways include short-term signalling of hunger and satiety to the central nervous system with hormones derived from the gastrointestinal tract, long-term signalling of energy stores to the brain via leptin and insulin, and control of metabolism. Rare genetic syndromes that present in early childhood with severe obesity (such as leptin deficiency and mutations in the pro-opiomelanocortin gene) demonstrate that these pathways are biologically important in humans. Most obesity develops as a result of modern lifestyles in genetically susceptible individuals. These changes include excessive consumption of high-energy food combined with low levels of physical activity; in many societies less affluent people seem to be most at risk. Other causes of obesity that should be considered include drugs that increase appetite and structural damage to areas of the central nervous system involved in appetite control, such as the hypothalamus.

Keywords Appetite; genetics; ghrelin; hypothalamus; leptin; metabolic rate; obesity; Prader–Willi syndrome; pro-opiomelanocortin; satiety

What's new?

- There has been increasing emphasis on measures of adiposity and fat distribution other than body mass index (particularly waist and waist–hip ratio) in relation to the metabolic consequences of obesity, leading some commentators to comment that BMI should be abandoned as a measure of adiposity[1–3]
- It has been recognized that a significant proportion of severe, early onset obesity may have a monogenic inheritance
- There has been progress with understanding the polygenic inheritance of obesity, with GWAS studies identifying over 75 new loci, including *FTO* and the associated *IRX3* genes
- Modern scanning methods have identified that brown adipose tissue is present in modest amounts in young, non-obese adults
- Recognition that homeostatic mechanisms can be overridden by strong environmental cues

Obesity develops when energy intake exceeds energy expenditure over time (usually many years), leading to accumulation of adipose tissue with a corresponding increase in lean body mass (from the necessarily enlarged muscle, bone and connective tissue). It is important to recognize that even a small daily energy imbalance eventually results in significant weight gain; for example, a daily excess of 100 kcal (equivalent to a small chocolate bar) leads to an increase of approximately 5 kg of fat over 12 months, or 50 kg over 10 years. The development of obesity, when it occurs, and its severity depend on a complex interaction of genetic and environmental influences. In general, severe obesity at a young age is more likely to be influenced by major genes affecting energy balance. Late-onset obesity, although influenced by minor genes, is more likely to have a strong environmental component.

Obesity is usually defined as a body mass index (BMI) of >30 kg/m^2 and overweight as >25 kg/m^2 but it may be considered pathophysiologically to be present when sufficient body fat has accumulated to adversely affect health. The occurrence of adverse effects may vary with populations, the distribution of the excess adipose tissue and the amount of muscle tissue; for example, excess fat in the abdomen and/or a relative lack of muscle (sarcopenic obesity) is associated with an increased risk of metabolic diseases such as diabetes mellitus. However, fat distribution may be less important for mechanical consequences such as osteoarthritis of the knee.

Regulation of energy balance

Energy balance is usually tightly regulated; even in societies where obesity is common, the average weight gain is only about 1 kg per year – reflecting an energy excess of about 20 kcal per day, or less than 1% of daily energy expenditure. This tendency to gain weight throughout adult life probably reflects the fact that the body's regulatory systems have evolved to protect against weight loss rather than prevent weight gain (see below). Food intake and energy expenditure are both under central nervous system control. Afferent neural and hormonal signals arise predominantly from the gastrointestinal tract, liver and adipose tissue, and efferent neural and hormonal signals influence the digestion and metabolism of food. There is probably a small capacity to 'burn off' excess calories through uncoupling of mitochondrial oxidation (see below); this is important in the brown adipose tissue (BAT) of rodents, and recent research has shown this also occurs in non-obese young adult humans. Thermogenesis occurs with weight loss in some pathological conditions (e.g. phaeochromocytoma), but the potential protective effect against obesity in humans remains uncertain.

Appetite regulation

Food intake is under short-term and long-term control.

- In the short term, hunger develops in response to decreasing circulating concentrations of glucose, fatty acids and possibly

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some amino acids. Ghrelin is secreted by the stomach between meals and stimulates food intake. Following a meal, concentrations of several 'satiety' hormones (e.g. cholecystokinin, glucagon-like peptide 1, oxyntomodulin, pancreatic polypeptide, peptide YY (3-36)) increase; with diminishing hunger signals, these act on the brain to stimulate a feeling of fullness and 'switch off' hunger.

- Longer-term signals depend mainly on stored fat, principally the adipocyte-derived hormone leptin. When adipose tissue mass is low and leptin concentrations decrease below a critical level, several powerful hunger signals are activated in the hypothalamus (Figure 1).

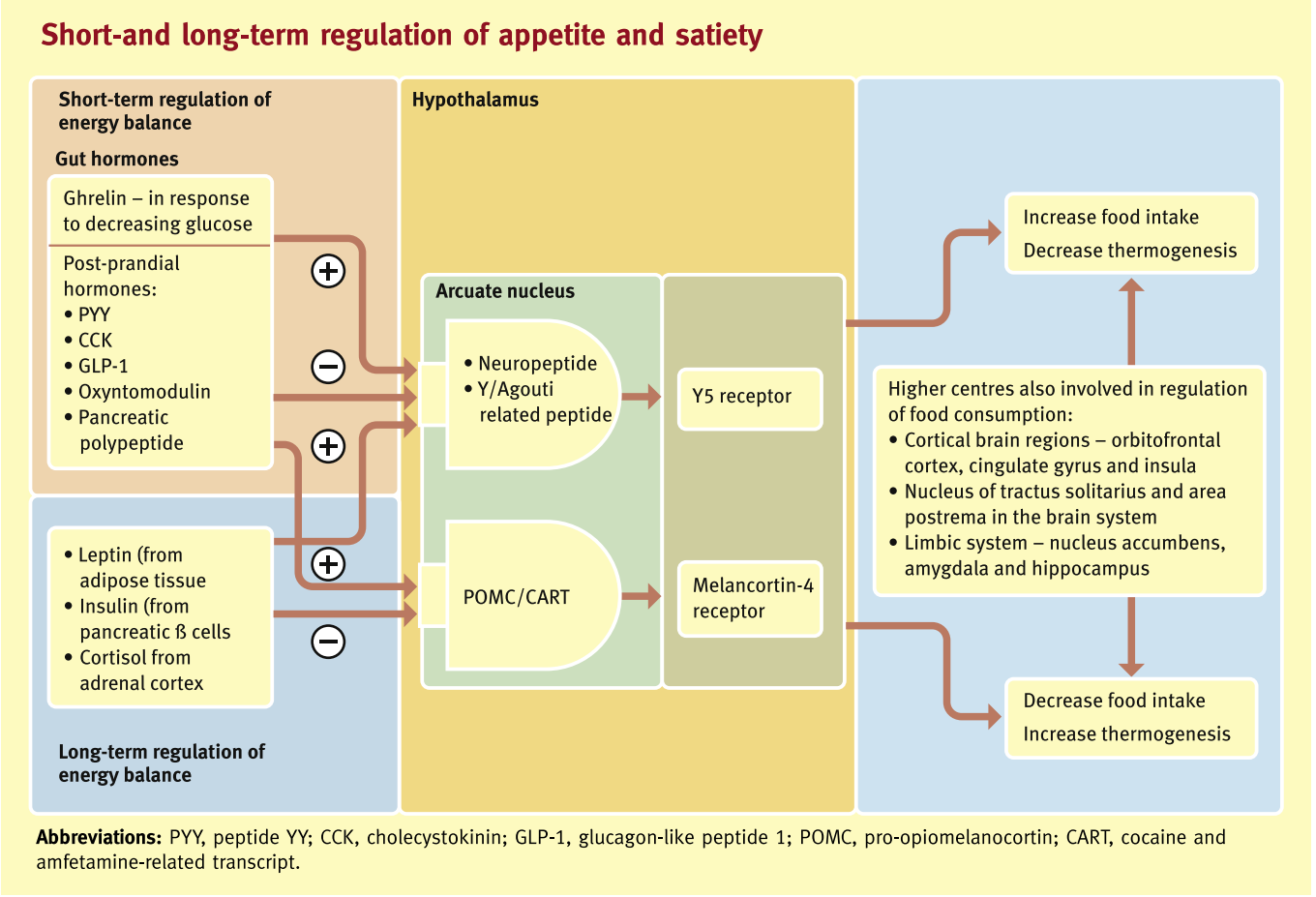
Role of the central nervous system (CNS)

Within the CNS, complex circuitry involving the brainstem, hypothalamus, limbic system and cortex respond to the circulating nutritional, neural and hormonal signals described above, determining feelings of hunger or satiety and thereby food intake, and influencing metabolic rate (via hormones and the sympathetic nervous system). Signals such as leptin (Figure 1) that decrease food intake tend to increase metabolic rate (favouring conservation of energy), and vice versa. Leptin concentrations in blood decrease when body fat mass decreases, activating hunger signals in the hypothalamus. Once fat mass increases again, this process is reversed, thereby maintaining body weight homeostasis. In general, it has been evolutionarily advantageous to maximize energy stores when food is plentiful. Other systems, including endogenous opiates and cannabinoids, may influence energy intake and the hedonic responses to food. Higher brain centres, including parts of the limbic system and cerebral cortex can override these homeostatic signals, which may partly explain why social and environmental cues (such as advertising) can easily overcome the normal regulatory system.

Regulation of metabolism

There are three principal components of energy expenditure: the basal metabolic rate, the thermic effect of food and energy consumed during physical work.

- The basal metabolic rate is the energy required to maintain normal metabolism. Under some circumstances, it is possible to 'uncouple' oxidative phosphorylation within mitochondria, dissipating excess energy as heat. In rodents, BAT is fat rich in mitochondria that are specialized for this purpose; uncoupling occurs following activation of BAT via the sympathetic nervous system (the β_3 adrenoceptor is specific to BAT). Activation of BAT is an important part of the response to cold, but it may also help determine ability to resist weight gain in response to overfeeding. There is evidence that this may also occur in humans, but there is controversy about the magnitude of the effect and whether it contributes to the tendency of some individuals to gain weight.



Abbreviations: PYY, peptide YY; CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; POMC, pro-opiomelanocortin; CART, cocaine and amfetamine-related transcript.

Figure 1