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L'ASSOCIATION CANADIENNE des MEDECINS et CHIRURGIENS BARIATRIQUE
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The Science of Obesity

David C. W. Lau MD PhD[i], Sean Wharton MD PharmD[ii]

i) Department of Medicine, Cumming School of Medicine, University of Calgary; Julia McFarlane Diabetes Research Centre; Libin Cardiovascular Institute of Alberta
ii) Michael G. DeGroote School of Medicine; McMaster University; The Wharton Medical Clinic; Adjunct Professor, York University

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Introduction

Obesity is a complex chronic disease in which abnormal or excess body fat (adiposity) impairs health, increases the risk of long-term medical complications and reduces life span. However, due to individual differences in body composition, body fat distribution and function, the threshold to which adiposity impairs health is highly variable among adults.[1] Epidemiological and population studies define obesity using the body mass index (BMI, weight/height^2). BMI is a fairly reliable anthropometric measurement to stratify obesity-related health risks at the population level. Obesity is operationally defined as a BMI exceeding 30 kg/m^2, and is subclassified into Class I (BMI 30–34.9), Class II (BMI 35–39.9) and Class III (BMI > 40).

Obesity is a chronic disease caused by the complex interplay of genetic, metabolic, behavioural and environmental factors; the latter are thought to be the proximal cause of the dramatic rise in the prevalence of obesity.[2] The increased availability of processed, affordable and effectively marketed food, abundance of sugar-sweetened beverages, economic growth, behavioural changes and rapid urbanization in low- and middle-income countries are some of the key drivers that promote overconsumption of food.[3] With respect to energy expenditure, the level of physical activity for leisure has been relatively stable or slightly elevated over the last 50 years.[4] This chapter attempts to address the cellular and molecular pathogenesis of obesity to inform a rational approach to management of this complex disease.

The neurobiology of appetite control and energy balance dysregulation

In states of energy imbalance, where food intake exceeds energy expenditure, the energy surfeit is converted into fat and stored in adipose tissue. Body weight is meticulously regulated for survival in unpredictable periods of feast and famine. Even a small surplus of caloric intake (less than 1%) over energy expenditure can accumulate over years to cause weight gain.[2]

The brain and obesity

The brain likely plays the most important role in obesity and energy balance. A simple approach to understanding the neurobiology of obesity may be to divide the brain into three main areas that regulate weight: the hypothalamus, the mesolimbic area and the cognitive lobe. Understanding the regulation of each area and the importance of the connections between these areas creates a greater understanding of obesity.

The hypothalamus (homeostatic area)

The brain, notably the hypothalamus, has long been known to play a central role in energy homeostasis by regulating energy intake and expenditure. Recent advances have provided newer insights into the complex control of appetite, with major implications for body weight regulation.[5–7]

The arcuate nucleus of the hypothalamus, often termed the hunger centre, controls feeding behaviours. There are two sets of neuronal population that reside in the arcuate nucleus. Neurons co-expressing agouti-related protein (AgRP) and neuropeptide Y (NPY) in the arcuate nucleus, when activated by hormonal and neural signals from the gut, adipose tissue and the peripheral organs, stimulate hunger sensation and trigger food-seeking behaviours.[8]

The activity of these neurons is rapidly reduced upon access to food. These neurons are primarily involved in food-seeking or the homeostatic control of appetite, but are less likely to normally drive food consumption. They mediate their downstream effects via the melanocortin-4 receptors located in the nearby paraventricular nucleus. The AgRP/NPY neurons project directly to the second set of neurons co-expressing pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), which suppress food intake by firing through the downstream inhibitory Y1 and gamma-aminobutyric acid (GABA) receptors.[8] The homeostatic control of appetite in the arcuate nucleus is influenced by a number of factors: the nutritional status of the organism, nutrient sensing and availability, taste, smell and food preferences.

The mesolimbic (hedonic area)

In addition to the homeostatic appetite control centre in the hypothalamus, other neural systems are involved and provide the emotional, pleasurable and rewarding aspects of eating, also known as hedonic eating. Hedonic eating is based on the feelings of reward and pleasure that are associated with seeing, smelling or eating food.[9] This pathway means that the brain can crave food, or enjoy food, even when the person is completely satiated. The signals are transmitted by the dopaminergic, opioid and endocannabinoid pathways via the respective receptors in the downstream targets.[10] Dopamine is released in the brain, signalling a desire to eat, in response to emotional triggers, such as sadness, or environmental triggers, such as the smell or sight of delicious food.[11] Opioid and endocannabinoid signals are released when food is consumed, and are responsible for the feeling of pleasure associated with eating.[12] Some people living with obesity may have a heightened anticipation (wanting) of the pleasure of food driven by a dysregulation of dopamine.[13] Unfortunately, the pleasure of eating the food (liking) is also dysfunctional and is downgraded compared to the anticipation, resulting in a need to overeat to achieve the level of the anticipation.[14] This leads to a vicious cycle and can create an environment of constant overeating. Controlling this dysregulation between wanting and liking with medications, hormonal regulation and cognitive behavioural therapy is a target for the treatment of obesity.

The lateral hypothalamus is a brain region that is tied to consummatory behaviours and mediates positive reinforcement.[15] These circuits drive food consumption and hedonic eating. Hedonic eating is also controlled by the corticolimbic system, which consists of cortical areas, basal ganglia, hippocampus and amygdala in the midbrain.[7]

The cognitive lobe (executive functioning)

The cognitive lobe is responsible for executive functioning and overriding primal behaviours driven by the mesolimbic system.[16] Cognitive functioning works well under optimal conditions (rest, oxygen, decreased stress and supports) that help to deal with adverse situations. Excessive eating often occurs in the evening, during suboptimal conditions, following the accumulation of stressors throughout the day, fatigue and lower levels of will power. There are also other areas of executive dysfunction in some people living with obesity, primarily in decision making, response inhibition and cognitive flexibility.[17] People living with obesity may have a dysfunctional connection between the cognitive lobe and the rest of the brain that leads to the inability to control eating behaviours.[16]

Current research indicates that there is significant crosstalk between homeostatic and hedonic eating, which is mediated by many of the endocrine and gut-derived signals. Leptin, insulin, ghrelin and glucagon-like peptide-1 (GLP-1) also act on the dopaminergic neurons in the midbrain to modulate food reward and hedonic eating.[18]

Another appetite-suppressing network involves calcitonin gene-related peptide (CGRP) neurons in the parabrachial nucleus (PBN) that potently suppress eating when activated, but these neurons do not increase food intake when inhibited. PBN-CGRP neurons are activated by signals associated with food intake, and they provide a signal of satiety that has negative valence when strongly activated.[7]

Recent data highlights that the hypothalamic circadian clock network is actively involved in the alignment of fasting and feeding with the sleep/awake cycle through the AgRP neurons by coordinating the leptin response and glucose metabolism with arousal.[19] Cognitive areas in the prefrontal cortex exert executive control on the decision to eat and the food choices.

In summary, the biological control of appetite is complex and involves the integration of the central neural circuits with signals from the gut, adipose tissue and other organs to influence homeostatic and hedonic eating, and the executive control by higher brain centres on the decision of when and what to eat. These neural networks have also been shown to be altered in obesity.

Adipose tissue and food intake

Leptin and insulin are the two key hormones that communicate to the homeostatic control of the long-term energy reserve and nutritional status in the body. Leptin is a fat-derived hormone that is secreted by white adipose tissue in proportion to the body's fat mass. Leptin and insulin bind to their respective receptors in the arcuate nucleus to decrease food intake and increase energy expenditure. In states of decreasing body fat stores, circulating leptin levels fall and signals the hypothalamus to inactivate the POMC/CART-expressing neurons to promote feeding, while simultaneously lowering its inhibitory effect on the AgRP/NPY-expressing neurons to increase appetite and decrease energy expenditure. As adiposity increases, leptin levels increase in the circulation and exert negative feedback to suppress appetite to prevent further weight gain. However, leptin resistance also occurs in some people who have excessive adiposity, which can perpetuate the vicious cycle of fat mass accretion.[20]

Gut-derived signals on nutrient availability

GLP-1, a powerful incretin, and peptide YY3-36 (PYY), which delays gastric emptying, are potent anorexigenic gut hormones that are

secreted by enteroendocrine L-cells in the small bowel in response to food ingestion. They both promote satiation (meal termination) and satiety by activating the POMC/PYY neurons while reducing hunger via the AgRP/NPY neurons. They communicate to the homeostatic system the prandial state and nutrient sensing and availability.[21] Oxyntomodulin is another peptide secreted concurrently with GLP-1 and PYY. Oxyntomodulin enhances satiety and decreases food consumption.[22]

Several other gut hormones are also involved in the control of appetite and energy expenditure. Cholecystokinin (CCK) is secreted in response to fat and protein ingestion. CCK stimulates gall bladder contractility and pancreatic enzyme secretion, and slows gastric emptying. CCK also mediates fat and protein satiation as well as glucose-regulatory effects on the hypothalamus, and also via the vagal afferent fibres. Pancreatic polypeptide (PP) is secreted by the F-cells in the pancreatic islets under vagal control and is released during the postprandial phase to enhance satiety.[22]

In contrast, ghrelin is an orexigenic hormone produced in the gastric fundus which increases hunger and stimulates food intake. Ghrelin level rises in the fasted state and falls rapidly following meal ingestion.

Upon food ingestion, sensory information on the volume and composition of the meals, and notably satiation, is relayed to the nucleus tract solitarius (NTS) in the brainstem by the vagal afferent fibres. The NTS in turn integrates and transmits the signals to the homeostatic control pathways in the hypothalamus, primarily influencing satiety and meal termination.[6]

Genes associated with obesity

The genetic and epigenetic variability among individuals influence how they self-regulate food and explains why not all people exposed to obesogenic factors develop obesity. Many genes have been linked to the development of obesity, and more than 140 genetic regions are now known to influence obesity traits.[23] Studies with twins have shown a relatively high degree of concordance of body mass and eating behaviours (50%–80%).[24] Linkage studies in rodents with obesity caused by single-gene mutations and candidate-gene-based approaches in humans with severe obesity have identified a number of mutations in genes involved in appetite control.[25] Loss of function mutations in leptin, leptin receptor, pro-opiomelanocortin and melanocortin receptor-4 are examples where individuals display intense hyperphagic and food-seeking behaviours. Correction of these rare defects, such as treatment of leptin-deficient participants with obesity with recombinant leptin, can result in significant weight loss.[26] Eleven monogenic forms of obesity have been discovered. They are rare, and the most common cause, heterozygous mutation in MC4R, accounts for about 2–5% of severe obesity in the pediatric population.[27] Most of these obesity-associated genes are found in the central nervous system and are mainly involved in the functional and structural aspects of neurotransmission. Syndromic forms of obesity are also uncommon; they include Prader-Willi, Bardet-Biedl and Cohen syndromes. Endocrine causes of obesity, such as Cushing disease, hypothyroidism and pseudohypoparathyroidism, are also rare and make up less than 1% of all cases of obesity.[28]

Adipose tissue and excess adiposity

Adipose tissue has long been viewed as a passive energy repository to store fat in the form of triglycerides, so that it can be released during periods of energy demand such as starvation or exercise. Adipose tissue is a dynamic organ that can respond to alterations in energy stores through adipocyte hypertrophy and hyperplasia. Adipose tissue can be as high as 50% of total body composition.[29] In adults, subcutaneous fat accounts for about 85% of total body fat, and intra-abdominal or visceral fat accounts for the rest. Within each fat depot, white adipose tissue is comprised of large mature adipocytes which account for about half of all cells, preadipocytes, endothelial cells, macrophages and inflammatory cells (up to 10% of cells). Adipose tissue expansion is accomplished via adipocyte hypertrophy, where cell size can increase up to seven-fold. Adipocyte hyperplasia relies on adipogenesis, which involves recruitment, proliferation and differentiation of preadipocytes to acquire the phenotype of mature adipocytes. Regulation of adipogenesis is meticulously controlled at the transcriptional level. The key players are CCAAT enhancer-binding proteins and peroxisome proliferating activator PPARg.[30] These transcription factors are subject to modulation by circulating hormones and nutrients, and they largely determine body fat distribution. Adipogenesis is associated with the production of a large number of proteins; many of these function as important signalling molecules in glucose and lipid metabolism, and energy homeostasis. Visceral fat is different from that of subcutaneous adipose tissue with regard to decreased insulin sensitivity, increased lipolytic activity, lower angiogenic potential, increased expression of proinflammatory adipokines and decreased production of the "good" hormones and cytokines.

Adipose-tissue-derived hormones and cytokines

Among the adipose-tissue-derived proteins, leptin and adiponectin have been extensively studied and provide new insights into adipose tissue biology and regulation. Leptin is secreted by adipocytes, and its plasma levels increase with weight gain and decrease with weight loss, in keeping with its key role as a signal of adipose tissue stores. Leptin binds to specific receptors, which belong to the interleukin-6 receptor family of class I cytokine receptors, and exerts inhibitory effect on food intake and appetite. Its effect is not limited to appetite regulation and energy homeostasis; it also exerts a wide array of endocrine and metabolic influences in the body. It suppresses insulin secretion from pancreatic β cells and plays a role in insulin resistance.[31]

Adiponectin is a hormone abundantly produced by adipocytes. It exerts pleiotropic effects on a broad array of physiological processes, including energy homeostasis, vascular function, systemic inflammation and cell growth. One of its most important functions

appears to be as an insulin-sensitizing agent which stimulates insulin gene expression and secretion. Adiponectin levels are inversely correlated in obesity and insulin-resistant states, and reflect whole-body insulin sensitivity. Circulating adiponectin levels are lower in people with obesity, polycystic ovarian syndrome, individuals with impaired glucose tolerance or type 2 diabetes. Decreased adiponectin level, or hypoadiponectinemia, is associated with increased risk for developing type 2 diabetes in otherwise healthy people.[20]

Adipose tissue dysfunction

Adipose tissue dysfunction may develop under conditions of continuous positive energy balance in people with an impaired expandability of subcutaneous adipose tissue. The inability to store excess calories in healthy subcutaneous fat depots can lead to increased visceral fat accretion and ectopic fat deposition in the liver, muscle and epicardium of the heart. Adipose tissue expansion often leads to dysfunctional changes, which are characterized by inflammation, inappropriate extracellular matrix remodelling and insufficient angiogenic potential. Cellular hypoxia is thought to be the driver for adipose tissue dysfunction.[32] A consequence of dysfunctional adipose tissue, especially in the visceral depots, is augmented production of fat-derived proinflammatory cytokines, or adipokines. These adipokines, which include tumour necrosis factor-α, interleukins, C-reactive protein and monocyte chemotactic protein-1, in turn can accelerate the progression to fibrosis, accelerated angiogenesis, apoptosis and autophagy by promoting the migration of immune cells into adipose tissue. Importantly, dysfunctional adipose tissue can lead to the development and progression of a myriad of adiposity-related comorbidities, such as type 2 diabetes, hypertension, dyslipidemia, nonalcoholic fatty liver disease, cardiometabolic risks and atherosclerotic cardiovascular disease.[33]

Brown and beige fat

Emerging data indicate that, in addition to white adipose tissue, brown adipose tissue, which is involved in whole-body energy homeostasis through non-shivering thermogenesis, also exists in small quantities in adult mammals and humans. Beige adipocytes, which are inducible forms of thermogenic adipocytes, have also been reported in white adipose tissue. Recruitment of beige adipocytes, or "beiging" of white fat, can be induced by chronic exposure to cold temperatures and, to some extent, exercise.[34] Further elucidation of the potential roles of brown/beige fat in the regulation of whole-body energy metabolism and glucose/lipid homeostasis will open new avenues for obesity management in the future.

Gut microbiome and obesity

The gut microbiota is the collection of all the micro-organisms in the gastrointestinal tract.[35] Recent data suggest that gut microbiota may influence weight gain and insulin resistance through different pathways, including energy harvesting from bacterial fermentation, short-chain fatty acid signalling and bile acid metabolism.[36]

The majority of the research in gut microbiota has been conducted in animal studies. These studies have determined that certain bacteria were responsible for promoting energy retention, and others for energy expenditure.[37] Human studies have indicated that the primary bacteria involved in weight homeostasis are the firmicutes that promoted weight gain and the bacteroidetes that are more often present in lean individuals.[38] Understanding the environments that would favour greater levels of firmicutes compared to bacteroidetes may to lead to greater understanding of the evolution of obesity, and possible treatments. Fecal transplants from lean individuals to those living with obesity have been conducted and are in their infancy but are already producing promising results in terms of insulin sensitivity and weight changes.[39] The use of prebiotics to alter gut flora in favour of bacteria that promote weight loss is also being investigated.[40] Surgery and medications may have an impact on the gut microbiomes, explaining some of the reasons for success with these interventions.[41,42] More data is leading us to understand that the gut microbiota interacts with the brain neurochemistry and that, in part, may influence weight changes.[43] This field is developing and may result in new interventions specifically targeted towards gut microbiota, but as yet there are few practical applications.

Adiposity-related medical complications

Adipose tissue dysfunction and excessive adiposity predispose to the development of many medical complications. The most common metabolic complication is insulin resistance and, in susceptible individuals, type 2 diabetes. The predominant theory between the link of obesity and cardiometabolic risk is described as obesity inducing an insulin resistant state through two primary mechanisms: a defective insulin signal, and chronic tissue inflammation and increased adipose tissue macrophages.[44] Adipose tissue is a source of increased levels of circulating free fatty acids due to increased lipolysis. In the liver, increased free fatty acid flux results in increased glucose production, triglyceride synthesis and secretion of very low-density lipoprotein. Other lipid abnormalities include reductions in high-density lipoprotein and increased levels of small dense atherogenic low-density lipoprotein particles. High levels of circulating free fatty acids are also taken up by muscle and the pancreas, and can lead to the development of ectopic fat. Free fatty acids impair insulin secretion in the pancreas and diminish insulin signalling in muscle and the liver, giving rise to insulin resistance in these organs.

It appears that adipose tissue from the visceral depot is more important as a source of excessive circulating adipokines and inflammatory mediators than the subcutaneous depots.[45,46] Importantly, inflammatory cells, such as macrophages and monocytes, migrate to visceral fat of subjects with obesity, further augmenting the inflammatory state, and impair insulin sensitivity.

Adiposity is also linked to increased risk for many forms of cancer through the release of hormonal growth factors and inflammatory adipokines.[47]

The obesity paradox

Despite the strong relationship between excess body fat and cardiometabolic risk, not all individuals who are living with overweight or obesity will develop diabetes or cardiovascular disease. A subset of people who are living with obesity are free of chronic diseases and cardiometabolic risk factors. These individuals were often referred to as "metabolically healthy subjects with obesity." The prevalence of the metabolically healthy subjects with obesity phenotype in the general population varies depending on the criteria used, and may be as high as 32%.[48] More recent data from the National Health and Nutrition Examination Survey (NHANES) III identified that only 40 of 1160 subjects with obesity in the study fulfilled the criteria of metabolically healthy subjects with obesity. Persons with the metabolically healthy phenotype were not at significantly increased risk of all-cause mortality, but their clinical risk profiles were worse than those of metabolically healthy lean individuals. On the other hand, some studies suggest the presence of an obesity paradox. Some people with excess weight (overweight) and those with Class I obesity (BMI between 30 and under 35 kg/m^2) might have a better prognosis with some chronic conditions, or lower mortality, than lean- or normal-weight unhealthy persons.[49] The obesity paradox has been reported in some patients with overweight and obesity with established cardiovascular diseases, such as heart failure, atrial fibrillation and peripheral artery disease. These individuals demonstrated a better prognosis than lean patients with the same diseases.[50]

Benefits of modest weight loss

Obesity management, as well as cardiorespiratory fitness, are critically important in improving the overall cardiovascular health of people who have overweight and obesity. Indeed, obesity management benefits all patients with obesity, regardless of the amount of weight loss. Patients able to achieve a weight loss of 5–10% of their initial weight will experience a reduction in their cardiovascular disease risk factors, improvement in lipid profiles, reductions in blood glucose and glycosylated hemoglobin and decreased risk for developing type 2 diabetes and other obesity-related complications.

The benefits of modest weight loss (5–10%) are worth emphasizing with respect to the prevention and management of type 2 diabetes. In the landmark National Institutes of Health-sponsored multi-centre Diabetes Prevention Program, 3234 participants living with overweight and obesity who also had impaired glucose tolerance were randomized to usual treatment (control) or to an intensive behavioural intervention. The aim was to achieve and maintain a reduction of 7% of their initial body weight through a -500 kilocalorie/day deficit hypocaloric diet and 150 minutes or more per week of moderate-intensity physical activity. A third group received metformin 850 mg twice daily. After a 2.8-year follow-up, the behavioural lifestyle intervention group lost 5.6 kg (6%) whereas the metformin group lost 2.1 kg (2.2%) and the control group lost 0.1 kg. Compared with the control group, the incidence of diabetes was reduced by 58% with behavioural intervention and by 31% with metformin.[51] The benefits of modest weight loss from the 2.8-years of intensive behavioural intervention persisted in the 10-year Diabetes Prevention Program Observation Study. The researchers concluded that each kilogram (1.1%) of body weight loss through intensive behavioural modification was associated with a 16% relative risk reduction in the development of type 2 diabetes in individuals with impaired glucose tolerance, and delayed the onset of disease by four years.[52] Metformin treatment was half as effective as intensive behavioural intervention and weight loss. A meta-analysis was undertaken of 17 randomized clinical trials on the effectiveness of behavioural intervention to prevent or delay diabetes. In over 8000 trial participants with impaired glucose tolerance, the pooled hazard ratio was 0.51 for behavioural intervention against standard counselling; this corresponded to numbers needed to treat for benefit of 6.4.[53]

Rational approach to obesity management

Interventions aimed at treating obesity and improving health through medical nutrition therapy and physical activity are the cornerstone approach for most people who have overweight and/or obesity. Medical nutrition therapy consists of reduced-calorie intake along with dietary patterns that have been shown to be effective in obesity management and for improving cardiovascular disease risk factors. Regular physical activity increases energy expenditure as well as improving cardiovascular health. Behavioural changes are by far the most important component for integrating successful eating and activity patterns over the long term. They may include self-monitoring or recording a food and exercise diary, peer support or individual or group counselling. Short-term behavioural changes lead to a modest weight loss of 3–5%, but is often difficult to sustain. Weight loss recidivism rates are high because our bodies are designed to resist weight loss. Reduction in energy expenditure and adaptive hormonal responses after weight loss may favour weight regain. A systematic review found that the mean rate of resting energy expenditure decreased by approximately 15 kcal/kg of weight lost, as observed in 2997 individuals; this decrease may be associated with body weight recidivism.[54] Moreover, after long-term diet-induced weight loss, levels of circulating hormones, such as leptin, insulin, GLP-1, CCK, PYY and ghrelin do not revert to levels recorded before weight loss and instead act to encourage weight regain.[55] The anorexigenic hormones (leptin, insulin, GLP-1) are reduced, whereas levels of the orexigenic hormone ghrelin are increased. Regular physical activity has been shown to be an integral component of long-term sustained weight loss.[56,57]

When behavioural interventions are not sufficient to meet obesity management health goals, psychological therapy, pharmacological therapy and bariatric surgery are treatment options that can facilitate and maintain the necessary weight loss and help prevent weight regain. Anti-obesity drugs, when used as adjunctive therapy to medical nutrition therapy and physical activity, can produce an additional average weight loss of 5–15%, depending on the drugs and the dosing. Bariatric surgery has rapidly emerged as a viable, realistic and successful long-term treatment option for

many patients living with severe obesity.[58] More recently, bariatric surgery has been advanced as a novel treatment option for patients who have obesity and type 2 diabetes.[59]

Conclusion

Obesity, or excess adiposity, is the result of an imbalance between energy consumption and energy expenditure by an individual. The causes of obesity are complex and result from interactions among biological, behavioural, psychosocial, genetic and environmental factors. A better understanding of the cellular and molecular pathways leading to the genesis of excess adiposity that impairs health will guide the practitioner to develop a rational approach to and management of this complex disease.

The summary of the Canadian Adult Obesity Clinical Practice Guideline is published in the Canadian Medical Association Journal, and contains information on the full methodology, management of authors' competing interests, a brief overview of all recommendations and other details. More detailed guideline chapters are published on the Obesity Canada website at www.obesitycanada.ca/guidelines.

Correspondence:
guidelines@obesitynetwork.ca

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