Pathophysiological Aspects of Human Obesity – What We Know in 2010

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Abstract
Obesity, a disease of both developed and developing countries, is spreading at an epidemic pace. According to the World Health Organization (WHO), obesity is defined as an increase or abnormal accumulation of body fat mass to the extent that an individual’s health will be negatively affected. Overweight (i.e. body mass index [BMI] >25kg/m²) is considered to be a significant risk factor for the development of many chronic diseases. Environmental, behavioural, genetic and biological factors interact to cause obesity, which can be viewed as a set of phenotypes that evolve over time in stages that need to be precisely measured. This article provides a clinical viewpoint on some biological processes that may explain some of the stages in the development of human obesity, its chronic maintenance and the occurrence of complications, with a focus on brain structures, genetics, the profound alterations in adipose tissue biology and the recent revival in thinking in terms of brown adipose tissue.

Keywords
Human obesity, chronic disease, adipokines, adipose organ, inflammation, environment, brown adipose tissue

The Natural History of Human Obesity
The accumulation of body fat in obese people indicates the failure of the body’s systems to ensure proper energy homeostasis by adjusting for environmental influences, behaviour, psychological factors, genetic make-up and neurohormonal status. While a body mass index (BMI) >30kg/m² is convenient to define obesity, this index does not take into account body composition (i.e. fat mass and fat-free mass distribution) and the natural history of a disease that evolves over time in a sequential manner. Obesity is a pathological deviation from the physiological evolution of fat mass over life (early growth, puberty, menopause, age, seasonal variation and ageing). One may schematically distinguish a ‘pre-obese static phase’ when the individual at risk of obesity is weight-stable and in energy equilibrium (i.e. fat mass and fat-free mass distribution) and the natural history of a disease that evolves over time in a sequential manner. Obesity is a pathological deviation from the physiological evolution of fat mass over life (early growth, puberty, menopause, age, seasonal variation and ageing). One may schematically distinguish a ‘pre-obese static phase’ when the individual at risk of obesity is weight-stable and in energy equilibrium, a ‘dynamic weight-gain phase’ during which weight is gained as a result of positive energy balance with energy intake exceeding expenditure and an ‘obese static phase’ when the individual is weight-stable again, but at a higher level, and energy balance is re-gained. These stages are rarely static. Weight fluctuates as a result of efforts to lose weight and return to initial weight. Weight fluctuations (the so-called ‘yo-yo syndrome’) correspond to the notion of weight cycling and frequently result in an even greater increase in weight. Resistance to weight loss and propensity to weight re-gain is a phenotype characterising chronic obesity. During the onset of obesity, minor energy imbalance can lead to gradual but persistent weight gain over time. The importance of the energy balance equation is well-documented; for example, an increase in energy intake of only 100kcal per day is sufficient to explain the average rate of weight gain in the past decade in the US. Depending on individual genetic background, behavioural and environmental factors are forces driving energy imbalance, and participate in energy storage in the adipose tissue (see Figure 1). Eating and physical activity patterns are obvious mediators influencing energy balance with high inter-individual and intra-individual variability. However, the adipose organ is not simply a site for passive energy storage. There are progressive biological alterations of this complex organ and perturbations of its dialogue with central (i.e. brain) and peripheral organs (i.e. muscle, intestine, liver, bone, vessels) via multiple signals. Once the obese state is established, the new weight is maintained by powerful biological and psychological regulators. In this article, we outline physiopathological components that participate in the different stages of human obesity, focusing on factors such as central nervous system structures, genetics and adipose tissues.

Central Structures Integrate and Orchestrate Various Signals
Neurohormonal circuits convey information about absorptive and post-absorptive periods, energy reserves, nutritional status, sensory inputs and the environment. There has been considerable improvement in...
the understanding of how neuronal circuitry integrates peripheral signals and regulates energy homeostasis. Hypothalamic structures relay complex networks of anabolic and catabolic effectors. These anabolic (i.e. promoting food intake, insulin release and decreased energy expenditure) and catabolic (with opposite actions) hormones and neurotransmitters are seen as part of a redundant system. While the concept of ‘feeding’ and ‘satiety’ centres developed in the 1950s proved overly simplistic, it allowed the identification of ‘first-order’ arcuate nucleus (ARC) and ‘second-order’ periventricular nucleus (PVN), dorsomedial and ventromedial nuclei (DMN, VMN) and lateral hypothalamic area (LH) peptideergic neurones, which play pivotal roles in controlling energy homeostasis. ARC neurones co-expressing pro-opiomelanocortin (POMC)-derived alpha-melanocyte stimulating hormone (αMSH) and cocaine- and amphetamine-regulated transcript (CART), which are peptides that reduce both food intake and energy storage, are considered as part of the first-order catabolic system. The catabolic circuit acts by inhibiting the activity of first-order anabolic neurones containing neuropeptide Y (NPY)/agouti-related peptide (AgRP) and acting on second-order neurones located in the PVN, VMN, DMN and LH. NPY and αMSH-containing terminals target two distinct second-order LH neuronal populations, namely the melanin-concentrating hormone (MCH) and the hypocretins/orxenes (ORX) neurones (see Figure 2). The melanocortin 4 receptor (MC4R) and one of its downstream effectors, brain-derived neurotrophic factor (BDNF), are pivotal in relaying information from the leptimelanocortin pathways. 5-hydroxytryptamine (5-HT) stimulates the catabolic circuits. The involvement of these neuronal systems is not restricted to feeding behaviour or energy expenditure, but also occurs more widely in the control of sleep/wakefulness and general arousal. At the molecular level, progress has been made in the examination of the transcriptional regulators, such as signal transducer and activator of transcription 3 (STAT3), forkhead box O1 (FOXO1) and signalling pathways (such as phosphoinositide 3-kinase [PI3K]/AKT) transmitting information from signals, such as leptin and insulin.

Since its discovery, the adipose-produced hormone leptin is seen as a master regulator that stimulates the catabolic system and inhibits the anabolic system. Other multiple signals participate in this regulation, including gut-derived hormonal and peptide signals (i.e. ghrelin-stimulating appetite, cholecystokinin, peptide PPY3-36 providing satiety signals, oxyntomodulin or endogenous steroids) and factors such as serotonin or epinephrine. Other substances that increase satiety signals, oxyntomodulin or endogenous steroids) and factors such as serotonin or epinephrine. Other substances that increase satiety signals, oxyntomodulin or endogenous steroids) and factors such as serotonin or epinephrine.

**The Burden of Genetics**

As emphasised by twin studies, genetic factors confer biological susceptibility on the effects of the environment and individual behaviour. Susceptibility may also result from intra-uterine or post-natal genetic imprinting. There is a wide spectrum ranging from genetically determined obesity to behaviourally determined obesity, with most individuals containing a mix of these factors (i.e. gene–environment interaction). At one end of the spectrum, there are genetically linked obese conditions characterised by severe and early-onset obesity associated with various combinations of behavioural (including hyperphagia, food seeking and impulsive behaviours), developmental, neurosensorial and endocrine disorders and dysmorphic features. The genetic basis of syndromic obesities (i.e. Prader-Willi and Bardet-Biedl syndrome [BBS]) is complex. Among the most fascinating results in this field is the discovery that BBS genes are linked to primary cilia dysfunction. The role of cilia cells in controlling central and eventually peripheral mechanisms of bodyweight regulation is still poorly understood. As naturally occurring mutations and the targeted disruption of genes in mouse models (leptin [LEP], leptin receptor [LEPR], POMC, melanocortin 4 receptor [MC4R] and melanocortin 3 receptor [MC3R]) were found to have pivotal roles in the same molecular pathway genes in and associated with the leptimelanocortin pathway were explored in targeted human cases. Mutations in genes encoding major proteins...
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**Figure 2: Hypothalamic Brain Structures Involved in Energy Homeostasis**

This is a schematic view of hypothalamic structures receiving multiple signals from the periphery. Light-blue arrows indicate catabolic systems while dark-blue arrow indicates anabolic system. *Genes in which rare human mutations have been found in leptin, leptin receptor (LEPR), pro-opiomelanocortin (POMC) and alpha melanocyte-stimulating hormone (αMSH), proconvertase hormone 1 (PC1) and 7b (neurotrophic tyrosine kinase, receptor, type 2) for NTRK2. A rare mutation has also been found in GHR (growth hormone receptor) expressed in neurons of the hypothalamic PVN. The expression of the solitary tract can directly receive signals from the gastrointestinal tract. The dorsal median nucleus is not represented here.*

**Figure 3: Body Mass Index Curve in Monogenic Forms of Obesity**

This figure illustrates the rapid and severe weight gain observed in French children with leptin receptor (LEPR) mutations (homozygous mutations) and either homozygous or heterozygous melanocortin 4 receptor (MC4R) mutations. The body mass index curve is characteristic of patients with monogenic obesity due to anomalies of the leptin/melanocortin pathway. 50P = 50th percentile; 97P = 97th percentile.

**Figure 4**

**Disease of the White Adipose Organ – Inflammation, Metabolic Dysfunction and Fibrosis**

Depending on the genetics of an individual, obesity reaching a plateau characterised in part by resistance to weight loss, propensity to weight re-gain and the appearance of complications. White adipose tissue (WAT) is composed of mature adipocytes, precursors (pre-adipocytes), endothelial cells, macrophages, mast cells, blood vessels, nerves and lymphatic and connective tissue. The phenotype, amount and biology of each WAT component are altered profoundly in chronic obesity (see Figure 4). In addition to adipocyte metabolic dysfunction (i.e. lipogenesis and lipolysis capacity), cellular stress including inflammation, oxidative reticulum endothelial stress and hypoxia are part of the biological alterations that attract and retain inflammatory cells within the WAT and promote adipocyte insulin resistance.

Fat cell plasticity is illustrated by the capacity of the adipocyte to expand significantly (hypertrophy) due to an increase in the amount involved in the leptin/melanocortin pathways indeed explain rare forms of monogenic obesity. MC4R mutations also influence early weight gain with various degrees of severity. Admittedly, obesity associated with MC4R mutations are the most common genetic forms of obesity. The frequency of human MC4R (hMC4R) mutations with in vitro functional consequences is relatively high (1.5–6%) in obese populations of European and North American origin. Unlike other monogenic obesities with individuals being carriers of homozygous or compound heterozygous mutations, most individuals are heterozygous carriers of mutated human MC4R (hMC4R) with an autosomal dominant inheritance, variable expression of obesity with age (i.e. from severe obesity to normal weight in MC4R-mutated carriers) and generational influences (i.e. children are more severely affected than their parents). The severity of obesity in these situations is illustrated by the BMI curve of LEPR and MC4R mutation carriers (see Figure 3).
of triglycerides contained in cell droplets. It is believed that beyond a threshold the cell can no longer enlarge, and increased fat storage requires an increase in the number of adipocytes (hyperplasia) and adipocyte differentiation. Fat hyperplasia involves the engagement of precursor cells that subsequently differentiate into mature adipocytes via a transcriptional programme; this is well-established in murine adipocytes but less so in human adipocytes. Once differentiated, adipocytes cannot recover their precursor state and remain available for fat storage even after losing weight. The amount of body fat cannot decrease below the level determined by the adipocyte number. The tightly regulated fat cell number is higher in obesity; however, the acquisition of adipocyte numbers appears to occur mainly from birth to early adulthood and remains constant thereafter. Obese adults are continually replenishing an existing larger pool of adipocytes. Cleverly using the integration of 14C derived from the nuclear bomb tests in adipocyte genomic DNA, Spalding et al. showed that approximately 10% of adipocytes in adults are renewed annually regardless of age or BMI.

WAT is an active endocrine and paracrine organ that synthesises regulators pivotal for body homeostasis, such as leptin, and releases energy substrates (i.e. fatty acids) to other organs when needed. Increased circulating inflammation molecules and decreased production of insulin-sensitising hormones such as adiponectin are hallmarks of obesity. While hypertrophic adipocytes synthesise inflammatory molecules, low-grade inflammation mainly relates to immune cells accumulating in obese WAT (see Figures 4 and 5). Macrophages, lymphocytes, natural killer cells and mast cells are found in human adipose tissue, but their cellular phenotype, kinetics of accumulation and precise role in the perturbation of WAT biology are not clear. There are discrepancies between rodent and human data. Macrophages, the most extensively studied cell in WAT, are increased in proportion to the amount of body fat and are more abundant in visceral than subcutaneous depots. Caspar-Bauguil et al. showed the modulation of T- and natural-killer-cell subtypes in animals that were subjected to a high-fat diet. There are discrepancies between rodent and human data. Macrophages, the most extensively studied cell in WAT, are increased in proportion to the amount of body fat and are more abundant in visceral than subcutaneous depots.

The evaluation of transcriptomic interactions characterising the adipose tissue of weight-stable obese subjects demonstrated the strong relationship linking inflammatory processes to extracellular matrix (ECM) remodelling components. For the first time, our group showed that interstitial fibrosis accumulates in obese WAT as in many organs affected by low-grade inflammation in chronic diseases (i.e. liver, lung, kidney pathologies). This observation was confirmed at the cellular level. WAT inflammation, mainly due to non-adipose cells, leads to major perturbations in pre-adipocyte biology, particularly the promotion of nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB)-dependent inflammation, ECM-component synthesis (such as fibronectin and collagens), the acquisition of migratory properties, increased proliferation and diminished differentiation (see Figure 4). The phenotypic modification of pre-adipocytes appears to be reversible in vitro when the inflammation stimulus is suppressed.

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Figure 4: Paracrine Cross-talk Between Macrophages, Adipocytes and Pre-adipocytes – Local and Systemic Consequences

Figure 5: Pathological Alterations of Human Adipose Tissue in Obesity

This work was the first demonstration of interstitial fibrosis in humans. Adipose tissue in obese subjects shows the accumulation of macrophages (panels A and B) and the presence of interstitial fibrosis (F; panels C and D) being more important in obese subjects. Panel E indicates fibrosis in non-obese adipose tissue while panel F indicates fibrosis in obese adipose tissue. Arrows indicate fibrosis. a = adipocyte; m = macrophages. References can be found in Kioephaphit M et al. and Lumeng CV et al.
While macrophages are suggested to clear necrotic adipocytes, adipocytes demonstrate profound modifications of their biology when co-cultured with macrophage medium. A pro-inflammatory state, increased lipolysis and resistance to insulin are observed (see Figure 4). Originally seen in muscle cells, reduced mitochondrial oxidative capacity may also occur in white adipose cells from obese subjects. The dynamics of WAT inflammation, metabolic alteration and ECM remodelling in the progression of human obesity remain unclear (see Figure 1). Increased interstitial fibrosis in WAT could impair cell-to-cell contact and therefore interfere with cellular signalling mechanisms that regulate adipogenesis and metabolic functions of WAT. As such, the appearance of fibrosis in the subcutaneous adipose tissue may perturb the adipocyte adipogenic capacity and lead to dysfunction in fat storage due to reduced capacity for adipose tissue expansion. It is well-known that the inability to properly store fatty acids in adipose tissue induces ectopic fat depots such as in muscle tissue and the liver and promotes insulin resistance. Accordingly, the consequence of the modulation of ECM rigidity has been illustrated by cell or mouse studies. The absence of membrane-type matrix metalloproteinase-1 (MMP1-MMP) leads to increased rigidity of ECM, diminished adipose expansion and lipodystrophy. By contrast, in genetically obese mice the deletion of collagen VI, a major component of ECM, favours adipose expansion and decreased inflammation and is associated with an improved metabolic profile.

**Revival of the Human Brown Adipose Tissue**

Brown adipose tissue (BAT) is characterised by its biological and anatomical properties (multilocular cells with numerous mitochondria) and significant capacity for oxidising lipids and dissipating energy as heat. BAT is essential for the control of core temperature and energy expenditure in rodents and newborns (relevant references in 57). In the 1970s, studies identified BAT in perirenal adipose tissue of children. Glycerokinase activity was reported to be higher in brown than adjacent WAT, suggesting its metabolic properties. With the exception of pathological conditions, such as pheochomocytoma or hibernoma or outdoor working conditions, the thermogenic role of BAT was considered negligible in adults. The recent findings of BAT in the neck in adult men and women, using positron-emission tomography and BAT-specific uncoupling protein-1 (UCP-1) staining, being negatively associated with amounts of adiposity and the fact that exposure to cold increased in vivo $^{2-18F}$ fluoro-2-deoxyglucose uptake into BAT suggests that BAT could be metabolically active.

Obese individuals have 25% decreased activation of this tissue after cold exposure. Women appear to have more active BAT than men. There is no doubt that these discoveries stimulate new avenues for understanding and treating obesity.

### Table 1: Example of Circulating Inflammatory or Adhesion Markers Modified in Human Obesity and Weight Loss

<table>
<thead>
<tr>
<th>Name</th>
<th>Systemic Modification</th>
<th>Effect of Weight Loss</th>
<th>Visceral versus Subcutaneous Adipose Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipokines/Adhesion Proteins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leptin</td>
<td>Elevation</td>
<td>Diminution</td>
<td>SC &gt; Vis</td>
</tr>
<tr>
<td>Visfatin</td>
<td>Elevation</td>
<td>Diminution</td>
<td>SC &gt; Vis (discussed)</td>
</tr>
<tr>
<td>Resistin</td>
<td>Diminution</td>
<td>Elevation or 0</td>
<td>Vis &gt; SC (discussed)</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Diminution</td>
<td>Elevation</td>
<td>SC &gt; SC</td>
</tr>
<tr>
<td>Omentin</td>
<td>Diminution</td>
<td>?</td>
<td>Vis &gt; SC</td>
</tr>
<tr>
<td>Adipokines/Adhesion Proteins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>Elevation</td>
<td>Diminution</td>
<td>Vis &gt; SC</td>
</tr>
<tr>
<td>Serum amyloid A</td>
<td>Elevation</td>
<td>Diminution</td>
<td>SC &gt; Vis</td>
</tr>
<tr>
<td>Macrophage migration inhibitory factor</td>
<td>Elevation</td>
<td>Diminution</td>
<td>Vis &gt; SC</td>
</tr>
<tr>
<td>Collagen VI</td>
<td>Diminution</td>
<td>Vis &gt; SC</td>
<td>Vis &gt; SC</td>
</tr>
<tr>
<td>Metalloproteinase matrix 9</td>
<td>Elevation</td>
<td>Diminution</td>
<td>–</td>
</tr>
<tr>
<td>Intercellular adhesion molecule</td>
<td>Elevation</td>
<td>Diminution</td>
<td>–</td>
</tr>
<tr>
<td>Vascular adhesion molecule</td>
<td>Elevation</td>
<td>Diminution</td>
<td>–</td>
</tr>
<tr>
<td>Hepatocyte growth factor</td>
<td>Elevation</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Plasminogen-activator inhibitor</td>
<td>Elevation</td>
<td>Diminution</td>
<td>Vis &gt; SC</td>
</tr>
<tr>
<td>Cathepsin S</td>
<td>Elevation</td>
<td>Diminution</td>
<td>Vis &gt; SC</td>
</tr>
</tbody>
</table>

SC = subcutaneous adipose tissue; Vis = visceral adipose tissue. The list is not exhaustive.

(IM Keophiphath, D Lacasa, unpublished data). While macrophages are suggested to clear necrotic adipocytes, adipocytes demonstrate profound modifications of their biology when co-cultured with macrophage medium. A pro-inflammatory state, increased lipolysis and resistance to insulin are observed (see Figure 4). Originally seen in muscle cells, reduced mitochondrial oxidative capacity may also occur in white adipose cells from obese subjects.
pursuing research on the molecular mechanisms controlling BAT-cell formation, such as the recently discovered role of the transcriptional factor PRDM16,\(^a\) with the objective of developing therapeutics that stimulate this metabolically active organ. Compared with WAT, after cold exposure human BAT expresses more PRDM16 as well as factors such as PGC1α, uncoupling protein 1 (UCP1), β3 adrenergic receptor (ADRB3) and DIO2 genes involved in BAT differentiation or metabolism.\(^b\) Studying more deeply the physiological contribution of BAT in energy balance equilibrium and its potential dysfunction in the development of obesity is under way in several research teams.\(^c\) Interestingly, it is possible to revisit the older and frequently debated approach, this study introduced the concept of lipokines, adipose-produced lipid-derived hormones that act at the systemic level. Such lipidomic approaches may be used to explore and better phenotype human adipose tissue depots. Other depots in the so-called ectopic sites may contribute to the production of inflammatory mediators in the absence of obesity. In this regard, the local production of the inflammatory molecules by the perivascular adipose tissue could contribute to the development of coronary pathologies.\(^d\)

### Somatic Consequences – Visceral Adipose Tissue, Fatty Acids, Adipokines and Lipokines as the Guilty Players

Obesity is associated with hypertension, diabetes, hyperlipidemia, coronary heart disease, liver disease, heart failure, respiratory failure, asthma, cholelithiasis, osteoarticular diseases, cancers and psychological disorders such as depression, which reduce the quality and length of life.\(^e\) Excess adipose tissue distribution in the upper part of the body conveys increased health risks, while excess adipose tissue in the lower part of the body is considered more metabolically healthy.\(^f\) Increased fatty acid release\(^g\) and perturbed secretion of adipose inflammatory molecules participating in the so-called low-grade systemic inflammatory response are pivotal in linking enlarged adipose tissue with obesity complications. Visceral adipose tissue, possessing distinct adipocyte functions and roles (lipogenesis, lipolytic activity, expression of developmental genes, hormonal response to insulin or to catecholamine, to sexual hormones or to cortisol)\(^h\) appears to be the deleterious organ. Stress\(^i\) and hormonal factors (such as glucocorticoids)\(^j\) promote the increased of visceral fat. Excess macrophages in visceral WAT may contribute to the risks associated with the accumulation of intra-abdominal fat, as illustrated by the association found between macrophage amount in the visceral fat and liver steatosis and fibroinflammation.\(^k\) WAT and liver pathology could involve increased free-fatty acid fluxes and/or delivery of pro-inflammatory factors to the liver through the portal circulation. Increased interleukin-6 (IL-6) concentrations measured in the portal vein of obese subjects suggest a role for this pro-inflammatory cytokine in promoting liver damage.\(^l\) Myriad adipokines (i.e. adipose secreted products) are proposed to be the guilty players\(^m\) (see Table 1).

Modest weight reduction improves the metabolic and cardiovascular risks associated with human obesity and is associated with improved systemic and adipose tissue inflammation.\(^n\)\(^o\)\(^p\) Since the pioneering work showing the influence of TNF-α in promoting insulin resistance,\(^q\) the influence of many adipokines on obesity-associated metabolic and cardiovascular complications is regularly updated.\(^r\) Decreased circulating adiponectin level is an important deleterious event for glucose metabolism and vessel homeostasis. Other molecules can also influence systemic metabolism, including the adipose-produced C16:1(n-7) palmitoleate. In addition to stimulating de novo lipogenesis and diminishing inflammation in the adipose tissue, palmitoleate acts in the liver to inhibit liver lipogenesis and improve muscle sensitivity to insulin.\(^s\) Based on a lipidomic approach, this study introduced the concept of lipokines, adipose-produced lipid-derived hormones that act at the systemic level.

### Towards ‘New’ Environmental Mediators Interacting with Biology

Genetic factors barely explain the dramatic increase in the prevalence of obesity. Social and economic factors such as academic achievement, job title and income correlate with obesity epidemics. Eating habits are crucial and numerous factors drive increased individual food intake, including availability and palatability of foods, visual and olfactory cues, conviviality, cultural attitudes, work-related eating habits and eating disorders. Caloric density of available foods, serving sizes and many other factors influence the risk of obesity.\(^t\) Although physical-activity-related energy expenditure is increased in obese compared with lean subjects, the habitual level of physical activity is classically lower in obese compared with lean subjects, and low physical activity levels (and increased sedentary behaviour) are associated with weight gain. On the other hand, increased bodyweight and obesity result in decreased physical activity; therefore, a complex and sometimes circular relationship occurs.\(^u\) We are now in uncharted territory: our traditional model for eating is not relevant for modern lifestyles and the profound changes in eating habits are not conducive to appropriate nutrition. As a result of changes in clothing, heating and means of transportation, we expend less energy than in the past; there has also been a decrease in the need for manual work and efforts to obtain food. Increased television viewing is associated with greater intake of energy-dense high-fat foods. Reduced sleep duration has been associated with obesity.\(^v\) While experts raise the point that the ‘obesogenic’ environment rather than the biology is the major player in obesity progression, these drivers are not mutually exclusive.\(^w\) Much more research needs to be carried out that examines the environmental stimuli promoting weight gain and their interaction with biological systems in promoting fat storage. In an elegant study, stress appeared to promote visceral fat gain and inflammation in mice via a mechanism involving the direct action of NPY on adipose tissue.\(^x\) Other factors such as pollutants, e.g. phthalates and organotins (produced by the plastic industry), interfere with the master regulators of adipogenesis, peroxisome proliferator-activated receptors (PPAR). Pollutants are not only endocrine disruptors acting on the receptive system, but are also considered metabolic disruptors.\(^y\) The importance of the linoleic acid/arachidonic acid/prostacyclin pathway in adipose tissue enlargement is suggested by the intriguing relationship observed between the dramatic increase in both the linoleic and arachidonic content of ingested fats and the increasing prevalence of overweight in infants in the last few decades.\(^z\) In the future, greater attention must be paid to the influence of micro-organisms such as bacteria (commensal bacteria in the gut composing the gut microbiota\(^{89}\)), viruses\(^{90}\) or various pollutants (persistent organic pollutants able to concentrate in adipose tissue).\(^{91}\) The discovery of a negative association between BAT amount and outdoor temperature raises the question of a link between global warming and the worldwide progression of obesity.
Conclusion

Understanding the natural history of obesity is a critical step towards developing effective interventions for both prevention and treatment of obesity. Human obesity involves complex physiopathological mechanisms that evolve over time and are largely beyond individual control. This complexity must be borne in mind when designing treatment strategies, considering the potential for disease progression and the heterogeneity of individuals with obesity.

With the enormous difficulties with central-nervous-system-affecting drugs in meeting safety recommendations, adipose tissue appears to be a tissue of choice for drug-target development to avoid progressive deterioration and to combat the complications of obesity.

Current Issues