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/m^2) 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

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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.[1] While a body mass index (BMI) >30kg/m^2 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 deviant from the physiological evolution of fat mass over life (early growth, puberty, menopause, age, seasonal variation and ageing).[2] 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 'yoyo 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;[3,4] 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.[4] 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. Human data are presented where possible. The contribution of organs such as liver or muscle in the pathogenesis of obesity, although critical, is marginally addressed as it is comprehensively reviewed elsewhere.[5]

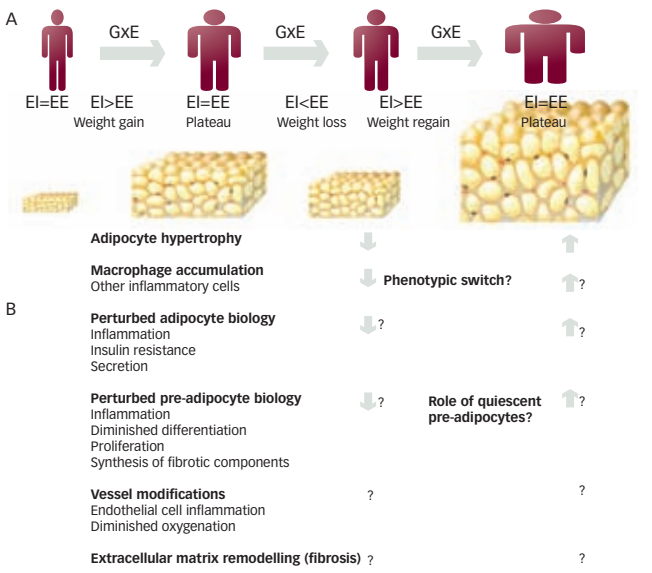
Central Structures Integrate and Orchestrate Various Signals

Neurohormonal circuits convey information about absorptive and post-absorptive periods, energy reserves, nutritional status, sensory inputs and the environment.[6] 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.[7] 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) peptidergic 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 neurons containing neuropeptide Y (NPY)/agouti-gene related peptide (AgRP) and acting on second-order neurons 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/orexins (ORX) neurons (see *Figure 2*).[8] The melanocortin 4 receptor (MC4R) and one of its downstream effectors, brain-derived neurotrophic factor (BDNF), are pivotal in relaying information from the leptin/melanocortin pathways.[7] 5-hydroxy-tryptamine (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.[6,7,9]

Since its discovery, the adipose-produced hormone leptin is seen as a master regulator that stimulates the catabolic system and inhibits the anabolic system.[10] Other multiple signals participate in this regulation, including gut-derived hormonal and peptidic 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 food intake are alpha2 catecholamine, opioids, the dopamine-dependent reward system and endocannabinoids, which increase the motivation to eat and contribute to the rewarding system. Neurons are also sensitive to food-metabolised nutrients (glucose, lipids, amino acids)[7,11] and inflammatory mediators via chemokines and cytokines.[12] POMC neurons are particularly responsive to glucose, promoting the release of αMSH[13] and becoming resistant to glucose in mice fed a high-fat diet. The modes of action for peripheral stimuli originating from both the gut/portal vein axis (hormones such as glucagon-like peptides, afferent vagal nervous fibres, portal glucose) and the bloodstream (variations in both nutrient and hormone concentrations, such as insulin and leptin) need to be further explored. For example, ORX seem more likely to contribute to short-term regulation of feeding in response to signals that originate from the periphery, such as glucose.[14] The molecular perturbations and adaptations during the natural evolution of obesity in the neuronal system (i.e. neuronal resistance to input signals such as leptin in so-called leptin resistance[10]) remain to be clearly understood in humans.

Figure 1: Schematic View of the Clinical History of Human Obesity – The Adipose Side

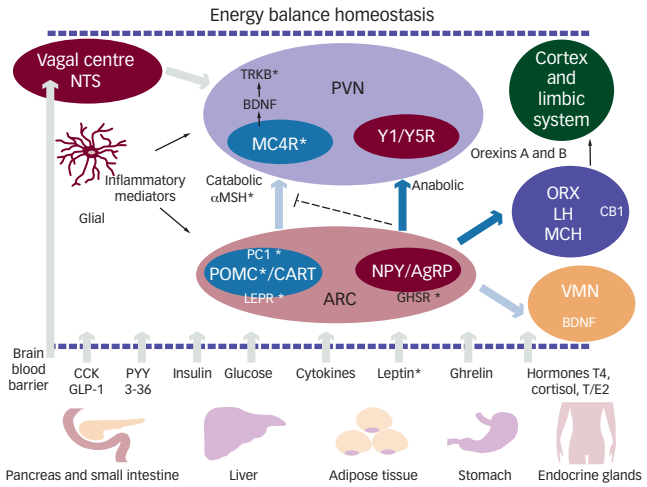


EE = energy expenditure; EI = energy intake; GxE = gene–environment interactions (environmental factors can be numerous).
A: Illustration of the natural history of obesity with the so-called 'yoyo syndrome'.
B: Summary of pathological alterations of adipose tissue components during human obesity evolution. Cell modifications have been studied in vitro *and much remains to be understood in humans, as indicated by the question marks. Based on* in vitro *findings, it is tempting to speculate that in the inflammatory environment, as found in the adipose tissue of weight-stable obese subjects, proliferating pre-adipocytes could further constitute pools of quiescent cells with a propensity to re-differentiate after weight loss, a situation known to be associated with diminished local inflammation.[75,76] This could favour relief of the inhibitory effect of macrophage-secreted factors on differentiation, as suggested by diminished macrophage accumulation and phenotypic change. The excessive weight re-gain commonly observed in clinical situations would be facilitated in response to usual external environmental solicitations (i.e. modified food intake and exercise). Nevertheless, this hypothesis has to be reconciled with the finding of a constant adipocyte pool at adult age. It is of particular importance to identify the mechanisms of macrophage accumulation and delineate their precise phenotype: pro-inflammatory M1 cells may diminish proliferation capacities, while by contrast an anti-inflammatory M2 state may promote differentiation of pre-adipocytes. Studies proposed a M2 phenotype of macrophages accumulating in human WAT.[88]*

The Burden of Genetics

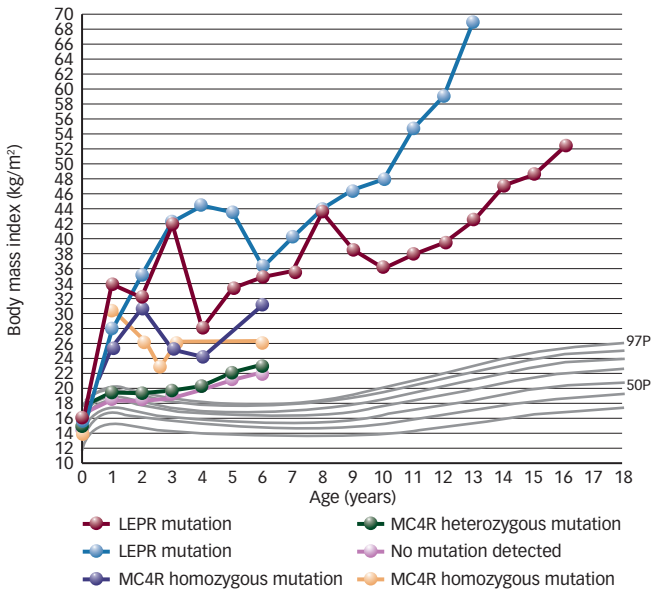
As emphasised by twin studies,[15] genetic factors confer biological susceptibility on the effects of the environment and individual behaviour.[16] Susceptibility may also result from intra-uterine or post-natal genetic imprinting.[17] There is a wide spectrum ranging from genetically determined obesity 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.[16,18] Among the most fascinating results in this field is the discovery that BBS genes are linked to primary cilia dysfunction.[19] The role of ciliated 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 leptin/melanocortin pathway were explored in targeted human cases. Mutations in genes encoding major proteins

Figure 2: Hypothalamic Brain Structures Involved in Energy Homoeostasis



*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 Trkb (neurotrophic tyrosine kinase, receptor, type 2 [or NTRK2]). A rare mutation has also been found in GHSR (ghrelin receptor) expressed in neuropeptide Y (NPY) neurons. The nucleus of the solitary tract can directly receive signals from the gastrointestinal tract. The dorso median nucleus is not represented here. AgRP = agouti-gene related peptide; ARC = arcuate nucleus; BDNF = brain-derived neurotrophic factor; CART = cocaine- and amphetamine-regulated transcript; CB1 = cannabinoid receptor; CCK = cholecystokinin; E2 = oestradiol; GLP1 = glucose-like peptide 1; LH = lateral hypothamus; MC4R = melanocortin 4 receptor; MCH = melanin-concentrating hormone; NTS = nucleus of the solitary tract; ORX = hypocretins/orexins neurons; PVN = paraventricular nucleus; PYY = peptide YY; T4 = thyroid hormone; T = testosterone; VMN = ventro median nucleus; Y1/Y5R = neuropeptide Y receptor. See reference 5 for further details.*

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.

involved in the leptin/melanocortin pathways indeed explain rare forms of monogenic obesities.[20] 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 autosomic 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).[16,20] The severity of obesity in these situations is illustrated by the BMI curve of LEPR and MC4R mutation carriers (see *Figure 3*).

While these mutated genes unambiguously influence the dynamics of weight gain in individual carriers, characterising the impact of genetic determinants on phenotypes of common forms of obesity is more complex. In recent months, considerable progress has been made in the understanding of the genetics of common obesity thanks to the rapid development of large-scale genetic screening (genome-wide association [GWA]) in large populations grouped in 'giantess' consortiums.[21] These approaches led to the identification of new chromosomal locations with single nucleotide polymorphisms (SNPs) potentially affecting an individual's corpulence. Huge numbers of individuals (30,000–80,000) were required for sufficient power to detect these genetic variants. However, this was at the expense of taking into account more specific body-composition measures and/or other more precise phenotypes. BMI was used and each variant allele explained a tiny proportion of its variance (from 0.05 to 0.24 BMI unit), with a modest but graded impact when variant alleles were combined (reviews in references 22 and in 23, in which the original articles can be found). Most implicated genes near 'guilty' SNPs have no known function, but these discoveries could pave the way to identifying new biological pathways in bodyweight regulation. Comprehensive approaches are needed to delineate the most important of the numerous phenotypes that geneticists will have to deal with when exploring inherited factors contributing to obesity and how to study them at the population level. The challenge is even greater for the exploration of the environmental influence on genetic backgrounds[24] and the interpretation of known genetic associations at the individual level (i.e. predictive significance).

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

Depending on the genetics of an individuals, obesity reaches 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.[25] 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),[26] cellular stress including inflammation, oxidative[27] reticulum endothelial stress[28,29] and hypoxia[30] are part of the biological alterations that attract and retain inflammatory cells within the WAT[31] and promote adipocyte insulin resistance.

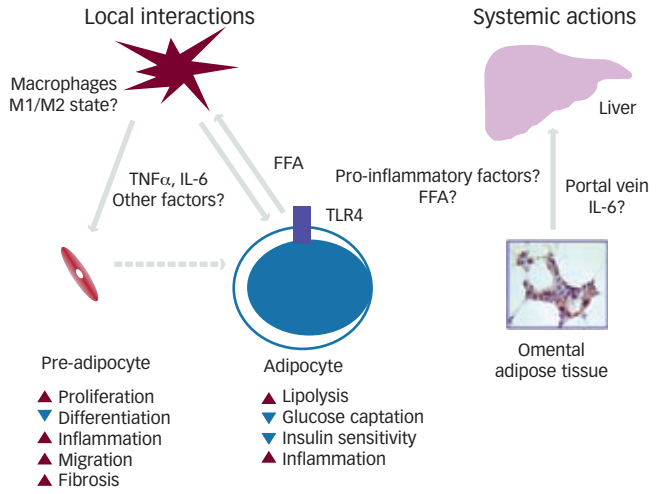
Fat cell plasticity is illustrated by the capacity of the adipocyte to expand significantly (hypertrophy) due to an increase in the amount

of triglycerides contained in cell droplets.[32] 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.[33] 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.[34,35] 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.[36]

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.[37] Increased circulating inflammation molecules and decreased production of insulin-sensitising hormones such as adiponectin are hallmarks of obesity.[38] While hypertrophic adipocytes synthesise inflammatory molecules,[39] 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.[40] 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[31,41] and are more abundant in visceral than subcutaneous depots.[42] Caspar-Bauguil et al. showed the modulation of T- and natural-killer-cell subtypes in animals that were subjected to a high-fat diet.[43] High-fat-diet-induced insulin resistance in rodents was associated with T-lymphocyte infiltration in the visceral depot, a phenomenon preceding macrophage recruitment.[44] Recent data suggest that mast cells are also important immune cells in WAT, as the absence of mast cells in transgenic mice leads to resistance to diet-induced weight gain and improved blood glucose tolerance.[45] The precise role of lymphocytes, NK cells and mast cells in WAT in humans needs to be elucidated.

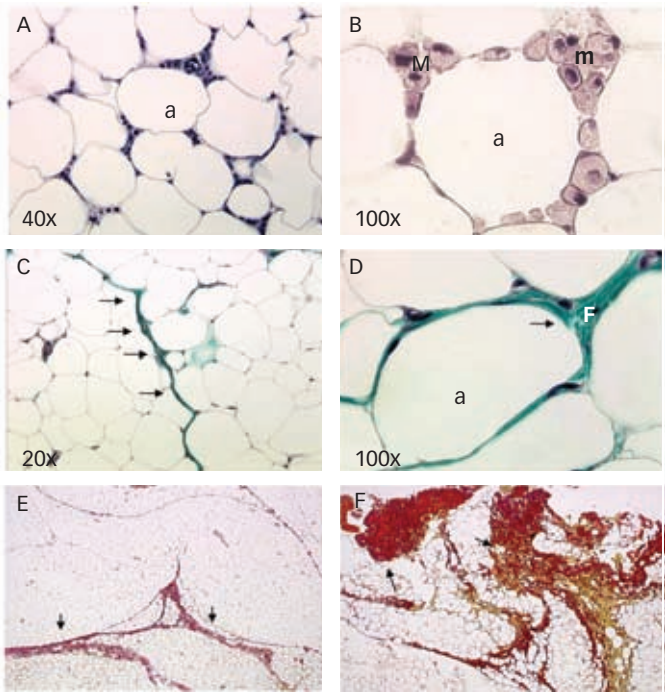
The evaluation of transcriptomic interactions characterising the adipose tissue of weight-stable obese subjects demonstrated the strong relationship linking inflammatory processes to extracellular matrix (ECM) remodelling components.[40] For the first time, our group showed that interstitial fibrosis accumulates in obese WAT[40] 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 (NFκB)-dependent inflammation, ECM-component synthesis (such as fibronectin and collagens), the acquisition of migratory properties, increased proliferation and diminished differentiation (see *Figure 4*).[46–48] The phenotypic modification of pre-adipocytes appears to be reversible *in vitro* when the inflammation stimulus is suppressed

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



It has been proposed in mice that while resident macrophages are of M2 (anti-inflammatory) phenotype, macrophages with a pro-inflammatory phenotype (M1) accumulate in adipose tissue of mice fed a high-fat diet.[90,91] Macrophages modify the biology of adipocytes and pre-adipocytes via the local production of adipokines. Tumour necrosis factor alpha (TNF-α) has been proposed to mediate some effects. The nuclear factor-kappa B (NF-κB) pathway implicated in the primary regulation of inflammatory responses is induced in pre-adipocytes and adipocytes in the presence of macrophages medium. The toll-like receptors (TLR4) expressed not only in macrophages but also in adipocytes, are important players leading to the induction or suppression of genes orchestrating the inflammatory response.[92] Free fatty acids produced by adipocytes after adrenergic stimulation are strong inducers of the TLR4/NF-κB pathway. Increased production of fatty acids by adipocytes activates TLR4 and perpetuates the inflammatory changes. TLR4 knockout mice are protected from these deleterious effects especially from insulin resistance induced by lipid infusions.

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 Keophiphath M et al.[47] and Lumeng CN et al.[89]

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

Name	Systemic Modification	Effect of Weight Loss	Visceral versus Subcutaneous Adipose Tissue
Non-specific Marker			
C-reactive protein	Elevation	Diminution	
Fibrinogen	Elevation	Diminution	
Orosomucoid	Elevation	Diminution	
Acute Phase of Inflammation			
Haptoglobin	Elevation	Diminution	Vis > SC
Serum amyloid A	Elevation	Diminution	SC > Vis
Cytokines/Interleukins			
Interleukin 6	Elevation	Diminution	Discussed
Interleukin 8	Elevation	Diminution	Vis > SC
Interleukin 18	Elevation	Diminution	Vis > SC
Interleukin 10	Elevation	Diminution	Vis = SC
Interleukin 1ra	Elevation	Diminution	Unclear
Tumour necrosis factor-alpha	Elevation	Diminution or 0	Vis = SC
Monocyte chemoattractant protein 1	Elevation	Diminution	Vis > SC
Monocyte chemoattractant protein 4	Elevation	?	?
Macrophage migration inhibitory factor	Elevation	Diminution	Vis = SC
Other Adipokines			
Leptin	Elevation	Diminution	SC > vis
Visfatin	Elevation	Diminution	Vis > SC (discussed)
Resistin	Diminution	Elevation or 0	Vis > SC (discussed)
Adiponectin	Diminution	Elevation	Vis > SC
Omentin	Diminution	?	Vis > SC
Adhesion Proteins/Extracellular Matrix Remodelling/Prothrombotics			
Metalloproteinase matrix 9	Elevation	Diminution	–
Intercellular adhesion molecule	Elevation	Diminution	–
Vascular adhesion molecule	Elevation	Diminution	–
Hepatocyte growth factor	Elevation	?	
Plasminogen-activator inhibitor	Elevation	Diminution	Vis > SC
Cathepsin S	Elevation	Diminution	Vis > SC

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

(M Keophiphath, D Lacasa, unpublished data). While macrophages are suggested to clear necrotic adipocytes,[49] adipocytes demonstrate profound modifications of their biology when co-cultured with macrophage medium.[50,51] A pro-inflammatory state, increased lipolysis and resistance to insulin are observed (see *Figure 4*). Originally seen in muscle cells,[51] reduced mitochondrial oxidative capacity may also occur in white adipose cells from obese subjects.[53–55]

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.[5] 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 (MTP1-MMP) leads to increased rigidity of ECM, diminished adipose expansion and lipodystrophy.[56] 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.[58] Glycerokinase activity was reported to be higher in brown than adjacent WAT, suggesting its metabolic properties.[59] With the exception of pathological conditions, such as pheochomocytoma or hibernoma or outdoor working conditions,[57] the thermogenic role of BAT was considered negligible in adults. The recent findings of BAT in the neck in adult men and women, using position-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-[^{18}F] fluoro-2-deoxyglucose uptake into BAT suggests that BAT could be metabolically active.[60–63]

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

pursuing research on the molecular mechanisms controlling BAT-cell formation, such as the recently discovered role of the transcriptional factor PRDM16,[64] 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.[60] 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.[57] Interestingly, it is possible to revisit the older and frequently debated studies showing genetic associations between UCP1 and ADRB3 polymorphisms, weight gain and obesity metabolic phenotypes.[65–67]

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

Obesity is associated with hypertension, diabetes, hyperlipidaemia, 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.[68]

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.[69] Increased fatty acid release[5] 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)[70] appears to be the deleterious organ. Stress[71] and hormonal factors (such as glucocorticoids)[72] 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.[42] 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.[73] Myriad adipokines (i.e. adipose secreted products) are proposed to be the guilty players[74] (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.[75,76] Since the pioneering work showing the influence of TNF-α in promoting insulin resistance,[77] the influence of many adipokines on obesity-associated metabolic and cardiovascular complications is regularly updated.[78] 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.[79] Based on a lipidomic 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.[80]

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.[81] 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.[82] 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.[83] 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.[4] 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.[71] 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.[84] 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.[33] 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[85]), viruses[86] or various pollutants (persistent organic pollutants able to concentrate in adipose tissue).[87] 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. ■

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