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Pathobiology of Obesity Adipose tissue evolved as a solution to the challenge of the intermittent availability of food. At times when food is plentiful, excess calories are converted to triglycerides and efficiently stored in the unilocular lipid droplets that occupy most of the volume of fat cells. When needed, the triglyceride is rapidly broken down to free fatty acids and glycerol, which provide an energy source to other sites throughout the body. However, in environments where food is abundant and when indi viduals tend to be sedentary, the chronic excess of energy intake over expenditure leads to obesity. The risks of developing obesity under those circumstances and of developing the illnesses associated with obesity vary greatly between individuals, with that variation having a strong genetic basis. ■ ■DEFINITION OF OBESITY AND OVERWEIGHT Obesity is defined as a state of excess adipose tissue mass that adversely affects health. The direct measurement of fat mass is not something that is readily undertaken in routine clinical practice, so a proxy mea sure, the body mass index (BMI), is generally used. This is calculated as weight/height2 (in kg/m2) (Fig. 413-1). BMI-based definitions of obesity and overweight have been established based on associations with certain morbidities and excess mortality. These definitions have been based largely on studies of predominantly white, Western popula tions, and there is

growing evidence that the relationship between BMI and adverse outcomes is different in people from other ethnic groups, usually in the direction of worse health outcomes being seen at lower levels of BMI. The World Health Organization (WHO) defines a BMI of 30 kg/m2 as the cutoff point for obesity, while individuals with values between 25 and 30 kg/m2 are classified as overweight. For individuals with a very muscular body habitus, the BMI may overestimate the

Body Mass Index (weight in kg/height in meters squared) Pathobiology of Obesity CHAPTER 413 Underweight <18.5 Normal weight 18.5–24.9 Overweight 25–29.9 Obese

> 30.0 FIGURE 413-1 Definitions of overweight and obesity. The World Health Organization defines obesity based on body mass index (BMI), which is calculated as weight in kilograms divided by the height in meters squared. amount of body fat. For any given BMI, women will generally have a higher percentage of body fat than men. The extent to which different adipose depots expand in response to chronic overnutrition varies markedly between people. In general, females store more fat in subcutaneous tissues, especially on buttocks, thighs, and upper arms, whereas men are more prone to store fat in intraabdominal and truncal subcutaneous sites. A simple measure of fat distribution is provided by a measurement of the waist-to-hip ratio. Independent of the degree of obesity, a waist-to-hip ratio >0.9 in women and >1.0 in men is associated with adverse health outcomes such as type 2 diabetes and dyslipidemia. ■ ■EPIDEMIOLOGY The annual National Health and Nutrition Examination Survey (NHANES) provides an ongoing record of the prevalence of obesity in the United States. In 2017–2018, 42.4% of U.S. adults aged ≥20 years old had obesity with no significant differences in prevalence by age group. Non-Hispanic black people had the highest prevalence of obesity at 49.6%, followed by Hispanic (44.8%), non-Hispanic white (42.2%), and non-Hispanic Asian (17.4%) people. In the United States, Asians repre sent a highly heterogeneous group encompassing both East and South Asia as well as a substantial Filipino community. The risks of obesity and its complications may differ greatly between people from different parts of Asia; in general, the prevalence of obesity is somewhat higher in women than in men, with black women having the highest preva lence at 56.9%. There has been a marked increase in the prevalence of obesity over time. For example, between 1976 and 1980, the NHANES survey reported a prevalence of 14.5%, indicating a near threefold increase over the past 40 years. This trend is seen globally. According to the WHO, obesity has nearly tripled worldwide since 1975. In 2016, >1.9 billion adults aged ≥18 years old were overweight. Of these, >650 million were obese; 39% of adults aged ≥18 years old were overweight in 2016, and 13% were obese. Most of the world’s population lives in countries where over weight and obesity kills more people than underweight. During this time, one of the most striking changes has been in the prevalence of obesity in children. In children, the relationship between BMI and body fat varies considerably with age and with pubertal maturation; however, when adjusted for age and sex, BMI is a reason

> able proxy for fat mass. Using age- and sex-specific BMI cutoffs (over weight ≥91st percentile; obesity ≥99th percentile), in 2019, the WHO estimated that 38 million children under the age of 5 were overweight or obese, and in 2016, they reported that 340 million children and adolescents aged 5–19 were overweight or obese. ■ ■PHYSIOLOGIC REGULATION OF ENERGY BALANCE Discussions about obesity so frequently focus on the issues of personal choice or the obesogenic environment that it can be easy to forget that

the amount of stored energy in our bodies is subject to homeostatic control by fundamental physiologic processes essential to our survival. In the 1940s, it was demonstrated that rodents defend their level of body fat; once returned to ad libitum diets after a short period of enforced caloric restriction or excess, animals either overconsumed or underconsumed calories until they returned to their previous status. Since that time, research has progressively dissected the signals that sense nutrient stores and the contents of our diets and how this infor mation is integrated to control hunger, satiety, and the expenditure of energy. The key locus for the integration of these signals is the hypo thalamus, an area of the brain at least partially outside the blood-brain barrier that facilitates its ability to receive hormonal signals and com bine these with sensory, cognitive, and other neural inputs.

PART 12 Endocrinology and Metabolism The hypothalamus receives multiple hormonal signals relevant to energy balance (Fig. 413-2). The circulating concentration of leptin, a peptide hormone produced by fat cells, increases as fat stores increase and declines as fat stores are depleted. Importantly, under conditions of caloric restriction, circulating leptin levels fall faster than the dis appearance of fat. Humans born without functional leptin or leptin receptors, although normal weight at birth, develop severe obesity from an early age, largely as a result of an intense drive to eat (hyper phagia). Clearly, a reduction of leptin below normal level is a powerful stimulus to food intake and largely explains the rebound overeating and weight regain that occurs after a period of starvation or diet ing. The hypothalamus also receives hormonal signals that are more Hypothalamus Leptin Ghrelin Adipose tissue GLP1 CCK Insulin Amylin PYY OXM Pancreas FIGURE 413-2 The homeostatic regulation of body weight. In most people, body weight remains stable over long periods of time despite fluctuations in the amount of food we eat and the amount of activity we undertake. This homeostatic regulation of body weight is controlled by the neurons in the hypothalamus, which receive hormonal signals from adipose tissue such as leptin and neural and hormonal signals from the gut in response to meals. Glucagon-like peptide 1 (GLP1) and cholecystokinin (CCK) from enteroendocrine cells of the small intestine and peptide YY (PYY) and oxyntomodulin (OXM) from the large intestine are secreted in response to eating a meal and/or the presence of nutrients in the intestinal lumen. Their release, together with neural signals from the vagus nerve and the enteric nervous system, contributes to satiety, acting on the hypothalamus via projections from the brainstem. Insulin, produced by the pancreas in response to carbohydrate- and protein-rich meals and potentiated by the action of some of the gut hormones, also has effects on the hypothalamic neurons controlling energy balance, whereas amylin acts predominantly via the brainstem. The release of the hormone ghrelin from the stomach increases in the unfed state and induces appetite by acting on hypothalamic neurons as well as on receptors in the brainstem.

immediately related to the amount and type of food that has been ingested. Peripheral hormones such as cholecystokinin (CCK) from the stomach, glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP) from enteroendocrine cells of the small intestine, and peptide YY (PYY) and oxyntomodulin from the large intestine are secreted in response to eating a meal and/or the presence of nutrients in the intestinal lumen. Their release together with neural signals from the vagus nerve and the enteric nervous system contributes to satiety, often indirectly acting on the hypothalamus via projections from the brainstem. Insulin and amylin, produced by the pancreas in response to carbohydrate and protein-rich meals, also have effects on neurons controlling energy balance. The propeptide pro-opiomelanocortin (POMC) is expressed in a highly restricted population of hypothalamic neurons that project widely throughout the brain (Fig. 413-3). These neurons are respon sive to the endocrine signals described above and are critical to the regulation of energy balance. The POMC-derived peptides α- and β-melanocyte-stimulating hormone (MSH) act on the melanocortin 4 receptor (MC4R) to regulate both food intake and aspects of energy expenditure that are influenced by the sympathetic nervous system. γ-MSH, acting mostly through the MC3 receptor, appears to play more of a role in controlling linear growth and the disposition of nutrients into lean versus fat tissues. Signaling through both these melanocortin receptors is also subject to negative control by a different population of neurons, which make and release agouti-related peptide (AGRP), neu ropeptide Y (NPY), and the inhibitory neu rotransmitter γ-aminobutyric acid (GABA). AGRP actively switches off melanocortin receptors. Leptin, which suppresses food intake, simultaneously stimulates POMC neurons and inhibits NPY/AGRP neurons. Human energy balance is highly sensitive to signaling through this system as people who have a genetic defect in just one of the two copies of the MC4R gene are very prone to overeat (hyperphagia) and to gain weight. Brainstem Vagus nerve ■ ■THE PHYSIOLOGY OF NUTRIENT STORAGE IN ADIPOSE TISSUE When energy intake exceeds energy expen diture, a small amount of that excess energy is stored as glycogen in liver and skeletal muscle. But if the imbalance is greater, then our bodies are designed to store that excess energy in a more efficient way as triacylglyc erol (triglyceride). This fat is more efficient because, unlike glycogen, it does not need accompanying water, and when metabo lized, it generates more than twice as much energy per gram than does carbohydrate. Adipocytes (fat cells) have evolved to contain a highly specialized organelle, the unilocu lar fat droplet, which holds the triglycer ide within a single-layer of phospholipid that contains all the components needed for enzymes that make and breakdown triglyc erides in a manner that is rapidly responsive to metabolic requirements. No other type of cell is specifically designed to store fat safely in this manner, and many of the adverse consequences of obesity are likely caused not by having too much fat in adipocytes but by “nonprofessional” cells being forced to take up and store fat. During weight gain, the amount of lipid in each fat cell increases. Some new fat cells can also be made in adult hood when ~10% of our fat cell population turns over every year.

Paraventricular nucleus Ventromedial nucleus BDNF MC4R α/β-MSH AGRP Arcuate nucleus POMC AGRP Hypothalamus LEPR LEPR Hypothalamus Leptin Adipose tissue FIGURE 413-3 Hypothalamic pathways regulating body weight. Neurons in the hypothalamus regulate energy intake and expenditure in response to leptin and other hormones. In the fed state, leptin stimulates primary neurons in the arcuate nucleus of the hypothalamus that express pro-opiomelanocortin (POMC). The POMC-derived peptides α- and β-melanocyte-stimulating hormone (MSH) act on the melanocortin 4 receptor (MC4R) expressed on neurons in the paraventricular nucleus to reduce energy intake and increase energy expenditure. At the same time, leptin inhibits neurons expressing agouti-related peptide (AGRP), which switches off melanocortin receptors. When these

and other key molecules, such as brain-derived neurotrophic factor (BDNF) and single minded-1 (SIM1), are disrupted by inherited mutations, affected individuals have hyperphagia and severe obesity. ■ ■THE CAUSES OF OBESITY: AN INTERACTION OF GENES AND ENVIRONMENT For a person to develop obesity, energy intake must exceed energy expenditure in a manner that is sufficiently sustained to result in the accumulation of a large excess of triglyceride in adipose tis sue. As obesity is a cumulative pathology, if energy intake exceeds energy expenditure by even a small amount (as little as 7 kcal/d), this is sufficient to develop obesity over a matter of years or decades. Even where obesity is common, there are many people who are not overweight. Economic and social factors are likely to play a role as there are more normal-weight people in wealthier and more socially advantaged groups, at least in Western societies. It is also true, however, that because of discrimination, people with obesity may become socially and economically disadvantaged, which complicates interpretation of that data. We can, however, state with considerable certainty that genetic factors play a major role in predisposing people to a range of adiposity. We know this from a large number of studies comparing identical and nonidentical twins. It is particularly telling that the degree of adiposity in adult life of identical twins brought up in different families is very similar between the twins but is not at all correlated with that of the adoptive siblings with whom they were raised.

■ ■THE RELATIVE ROLES OF EXCESS INTAKE AND LOWER ENERGY EXPENDITURE IN CONFERRING BIOLOGIC PREDISPOSITION Do these heritable factors influence energy intake, energy expenditure, or both? It is clear that by the time a person develops obesity the amount of energy they expend in the resting state is more, not less, than a normal weight person. However, if a person with obesity loses weight by dieting, there is some evidence that they tend to be more “energy effi cient” than a person who has never been obese, particularly in terms of how many calories they burn during a defined bout of activity. However, the effects are subtle. It seems very likely that there are some individuals who are predominantly pre disposed to develop obesity by virtue of a lower metabolic rate, but thus far, apart from severe hypothyroidism, concrete examples are scarce. In contrast, a much more consistent and compelling body of evidence supports the idea that the genetic predisposition to obesity is largely mediated through the brain’s control of food intake. When studied in controlled settings, individuals who carry genetic variants that predispose to obesity tend to eat more and be less readily satiated. This is very readily demonstrable when the mutation has a major effect on obesity predisposition, but similar data are now emerging in the case of common genetic variants with smaller effects.

Reduced food intake Increased energy expenditure Pathobiology of Obesity CHAPTER 413 SIM1 ■ ■ENVIRONMENTAL FACTORS PREDISPOSING TO OBESITY Obesity cannot exist in the absence of sufficient food to lay down and maintain excess fat stores. That fact not infre quently leads to the belief that the prin cipal cause of obesity must be either a person’s ignorance of the role of excess caloric intake or their conscious choice to prioritize the immediate pleasures of eating over the long-term health harms associated with obesity. Taken to extremes, these views can engender serious social, economic, and medical discrimination against people with obesity. It is clear that genetic factors, however important they are in an individual’s predisposition to obesity, cannot explain the marked increase in obesity prevalence that has occurred in the past few decades. We have to look to an environment that has become increas ingly obesogenic to explain that phenomenon. In most developed and developing countries, energy-dense and highly palatable food and beverages have been aggressively marketed, made cheaper than ever before, provided in

larger portions, and made available ubiquitously and continuously. This has been combined with the reduction in physi cal activity in work and domestic life due to mechanization and the change in the nature of employment. Even the control of our external temperature by artificial heating and cooling has meant less energy expended on thermoregulation. Taken together, these are likely to be the major factors driving the recent increase in obesity. It is important to remember, however, that a substantial proportion of the population remains normal weight under these circumstances and a large part of that is attributable to their genetic good fortune. There is much current investigation into other environmental fac tors that might influence the development of obesity. Heated debates

continue about the optimal balance of macronutrients in the diet to maintain normal weight and good health. Much of this revolves around the potential benefits of reducing the relative proportion of carbohydrates in the diet (Chap. 414). There seems to be reasonable consensus that, in the short term, diets that are rich in protein and fat and lower in carbohydrates more readily result in quick weight loss. This may be because the appetite-suppressing gut hormones discussed above increase more in response to protein than to carbohydrate, thus inducing earlier satiation. However, longer-term studies to date are less compelling, and the long-term increases in protein and fat intake are not without at least theoretical risks. A growing body of evidence suggests that exposures early in life, either in utero or in early postnatal life, might “program” individuals to develop obesity and/ or cardiometabolic disease through effects that are often attributed to “epigenetics” (Chap. 497). This is an attractive idea, and if true, it would mean that time-limited and affordable interventions early in life might have lifelong benefits. Inevitably, it will take time to see if the promise of such interventions will be fulfilled. Much excitement has been generated by the increasing recognition of the diversity of our intestinal microbiome, which clearly has relevance to gastroin testinal health (Chap. 484). At present, it is premature to ascribe any significant role to the human microbiome in obesity or its adverse consequences.

PART 12 Endocrinology and Metabolism ■ ■WHY DOESN’T LEPTIN PREVENT OBESITY? Leptin is known to suppress food intake, and its levels rise as fat stores expand. So why does this not prevent us from developing obesity? The most plausible explanation lies in the evolutionary history of leptin and the fact that it appears to defend strongly against the loss of body fat stores, with a fall in circulating leptin below a person’s habitual level being a powerful stimulus to food intake, whereas the response to rises in leptin above the normal level is less pronounced. At higher levels of leptin, administering extra amounts of the hormone may have no discernible effect at all—a phenomenon that has come to be called leptin resistance. It is important to remember that even though a person appears to be leptin resistant, some leptin action is occurring; otherwise, the person would become as insatiably hungry and progres sively obese as someone with congenital leptin deficiency (see below). It also seems likely that a subgroup of people may have relatively low leptin levels, which plays a role in the etiology of their obesity. There are likely other hormonal signals produced in severe obesity that, unlike leptin, continue to exert a suppressive effect on food intake and help to ensure that the expansion of adipose tissue does not become indefinitely cumulative. ■ ■SINGLE-GENE DISORDERS LEADING TO OBESITY The assessment of severely obese children and, indeed, adults should be directed at screening for potentially treatable endocrine and neuro logic conditions and identifying genetic conditions so that appropriate genetic counseling and, in some cases, treatment can be started. Clini cally, it remains useful to categorize the genetic obesity syndromes as those with dysmorphism and/or developmental delay and those with out

these features (Tables 413-1 and 413-2). Although individually these monogenic disorders are rare, cumulatively, up to 20% of chil dren with severe obesity have rare chromosomal abnormalities and/or highly penetrant genetic mutations that drive their obesity. This figure is likely to increase with wider accessibility to genetic testing and as new genes are identified. A genetic diagnosis can inform manage ment (many such patients find it very difficult to lose weight through diet and exercise) and can inform clinical decision-making regarding the use of bariatric surgery (feasible in some; high risk in others) (Chap. 414). There are a number of drugs in clinical trials targeted specifically at patients with genetic obesity syndromes. Specifically, setmelanotide, a MC4R agonist, has been used effectively in phase 2/3 clinical trials in children who are genetically deficient in POMC, PCSK1, and the leptin receptor. It is also being explored for the treat ment of other genetic obesity syndromes affecting the melanocortin pathway and in acquired hypothalamic obesity caused by tumors such as craniopharyngiomas.

TABLE 413-1 Classical Genetic Obesity Syndromes ADDITIONAL CLINICAL FEATURES SYNDROME INHERITANCE Prader-Willi Autosomal dominant Hypotonia, failure to thrive in infancy, developmental delay, short stature, hypogonadotropic hypogonadism, sleep disturbance, obsessive behavior Albright’s hereditary osteodystrophy or pseudohypoparathyroidism Autosomal dominant Short stature in some, skeletal defects, developmental delay, shortened metacarpals; hormone resistance when mutation on maternally inherited allele Bardet-Biedl Autosomal recessive Syndactyly/brachydactyly/ polydactyly, developmental delay, retinal dystrophy or pigmentary retinopathy, hypogonadism, renal abnormalities Cohen’s Autosomal recessive Facial dysmorphism, microcephaly, hypotonia, developmental delay, retinopathy Carpenter’s Autosomal recessive Acrocephaly, brachydactyly, developmental delay, congenital heart defects; growth retardation, hypogonadism Alström’s Autosomal recessive Progressive cone-rod dystrophy, sensorineural hearing loss, hyperinsulinemia, early type 2 diabetes mellitus, dilated cardiomyopathy, pulmonary, hepatic and renal fibrosis Tubby Autosomal recessive Progressive cone-rod dystrophy, hearing loss ■ ■CLASSICAL SYNDROMIC DISORDERS A number of syndromes were identified by clinicians long before their exact genetic cause was known. In these syndromes, obesity is associated with a stereotyped set of other anomalies, often neurode velopmental in type. The precise genetic basis for the majority of these syndromes is now known. Prader-Willi syndrome (PWS) is the most common syndromic cause of obesity, with an estimated prevalence of ~1 in 25,000. It is an autosomal dominant disorder caused by deletion of an imprinted region on the paternal chromosome 15 (Chap. 479). The characteristic clinical features are hypotonia, feeding difficulties in infancy, developmental delay, hypogonadotropic hypogonadism, hyperphagia (increased food intake), and obesity. Children with PWS are short with reduced lean body mass and increased fat mass, fea tures resembling those seen in growth hormone (GH) deficiency; GH treatment decreases body fat and increases linear growth and muscle mass and is now standard of care in this condition. Low levels of brain expression of the neuropeptide oxytocin and the nerve growth factor brain-derived neurotrophic factor (BDNF) in PWS patients have sug gested new therapeutic opportunities for these patients. Inherited or de novo (not found in either parent) mutations in another imprinted gene, GNAS1, which encodes Gsα protein, cause a syndrome known as Albright’s hereditary osteodystrophy (AHO) or pseudohypoparathyroidism (PHP) (Chap. 424). Maternal trans mission of GNAS1 mutations leads to short stature, obesity, and skeletal defects plus resistance to several hormones (e.g., parathyroid hormone), whereas paternal transmission leads only to the AHO phe notype. The clinical spectrum is very broad, and some patients may present with obesity alone. Bardet-Biedl syndrome (BBS) is a rare autosomal recessive dis ease characterized by

obesity, developmental delay, polydactyly, reti nal dystrophy or pigmentary retinopathy, hypogonadism, and renal

TABLE 413-2 Obesity Syndromes due to Mutations in Genes Controlling Energy Homeostasis Pathways GENE AFFECTED INHERITANCE ADDITIONAL CLINICAL FEATURES Leptin Autosomal recessive Severe hyperphagia, frequent infections, hypogonadotropic hypogonadism, mild hypothyroidism Leptin receptor Autosomal recessive Severe hyperphagia, frequent infections, hypogonadotropic hypogonadism, mild hypothyroidism Proopiomelanocortin Autosomal recessive Hyperphagia, cholestatic jaundice or adrenal crisis due to ACTH deficiency, pale skin and red hair Prohormone convertase 1 Autosomal recessive Small-bowel enteropathy, postprandial hypoglycemia, hypothyroidism, ACTH deficiency, hypogonadism, central diabetes insipidus Carboxypeptidase E Autosomal recessive Severe insulin resistance Melanocortin 4 receptor Autosomal dominant Hyperphagia, accelerated linear growth Single-minded 1 Autosomal dominant Hyperphagia, accelerated linear growth, speech and language delay, autistic traits BDNF Autosomal dominant Hyperphagia, developmental delay, hyperactivity, behavioral problems including aggression TrkB Autosomal dominant Hyperphagia, speech and language delay, variable developmental delay, hyperactivity, behavioral problems including aggression SH2B1 Autosomal dominant Hyperphagia, disproportionate hyperinsulinemia, early type 2 diabetes mellitus, behavioral problems including aggression Abbreviations: ACTH, adrenocorticotropic hormone; BDNF, brain-derived neurotrophic factor; SH2B1, Src-homology-2 (SH2) B-adaptor protein-1 (SH2B1); TrkB, tropomyosin receptor kinase B. abnormalities. The same clinical features can arise from mutations in >26 genes, which disrupt signaling in primary cilia. Melanocortin receptor agonists may be useful in treating hyperphagia and obesity in patients with BBS. Overlapping clinical features are seen in a number of other genetic obesity syndromes (Table 413-1). ■ ■DISORDERS OF LEPTIN-MELANOCORTIN SIGNALING Homozygous mutations that disrupt the production or action of leptin are rare but result in a disorder that is treatable. Children with homo zygous loss-of-function leptin mutations have rapid weight gain in the first few months of life, resulting in severe obesity due to an intense drive to eat (hyperphagia) and impaired satiety with food-seeking behavior soon after the end of a meal. Congenital leptin deficiency can be treated with subcutaneous injections of recombinant leptin, which reduce hunger, increase satiety, and lead to weight loss. Similar clinical features are seen in patients with homozygous mutations in the leptin receptor gene, but they are not responsive to leptin treatment (Table 413-2). Normal pubertal development rarely occurs in adults with leptin or leptin receptor deficiency, with biochemical evidence of hypogonadotropic hypogonadism. However, there is some evidence for the delayed but spontaneous onset of menses in a small number of leptin- and leptin receptor–deficient adults. Leptin treatment per mits progression of pubertal development, suggesting that leptin is a permissive factor for the development of puberty. An MC4R agonist (setmelanotide) is licensed for chronic weight management in leptin receptor deficiency. Homozygous or compound heterozygous mutations in POMC lead to hyperphagia and early-onset obesity. As adrenocorticotropic hormone (ACTH) is produced in the pituitary gland by cleavage from POMC, patients also present with isolated ACTH deficiency (neonatal

hypoglycemia and cholestatic jaundice). In the skin, POMC-derived melanocortin peptides act on melanocortin 1 receptors to induce pigmentation. For this reason, the lack of POMC-derived peptides in obese patients with POMC deficiency results in hypopigmenta tion of skin and hair, which is more noticeable in people of Caucasian ancestry who often have red hair. Prohormone

convertase 1 (PCSK1) is an enzyme involved in the cleavage of POMC into ACTH, which is then further cleaved to make α-MSH by carboxypeptidase E. Impaired processing of POMC contributes to the hyperphagic severe early-onset obesity and ACTH deficiency in people lacking PCSK1 who also have hypogonadotropic hypogonadism, postprandial hypoglycemia (due to impaired processing of proinsulin to insulin), and a neonatal enteropathy in early childhood. Heterozygous mutations that impair the function of MC4R are found in 5–6% of patients with severe earlyonset obesity and at a frequency of ~1 in 300 in the general population, making this the most common gene in which variants contribute to obesity. MC4R mutations are inherited in a co-dominant manner, with variable penetrance and expression in heterozygous carriers; homozy gous carriers are severely obese. Patients are often hyperphagic from early childhood and hyperinsulinemic and have increased lean mass and increased linear growth.

Pathobiology of Obesity CHAPTER 413 ■ ■GENETIC SUBTYPES OF OBESITY ASSOCIATED WITH NEUROBEHAVIORAL ABNORMALITIES Both PWS patients and patients with mutations in SIM1 (a gene that acts downstream of MC4R) exhibit a spectrum of behavioral abnor malities that overlap with autism-like features that could be related to reduced oxytocin signaling (Table 413-2). Mutations affecting BDNF and its receptor tropomyosin receptor kinase B (TrkB) cause speech and language delay, hyperphagia, and severe obesity, as well as hyperactivity, autistic traits, and impaired short-term memory. Interestingly, a com mon variant in BDNF (V66M), found in heterozygous form in ~20% of the population, is associated with a number of traits and neuropsychi atric disorders including anxiety and depression. Chromosomal deletion and mutations affecting Src-homology-2 (SH2) B-adaptor protein-1 (SH2B1) are associated with dominantly inherited, severe, early-onset obesity, disproportionate insulin resistance, early-onset type 2 diabetes, and behavioral problems including aggressive behavior. ■ ■OBESITY SECONDARY TO OTHER DISORDERS Endocrine Disorders Patients with hypothyroidism may gain weight and develop obesity, although it is rarely the sole cause of severe obesity. It is nonetheless prudent always to measure thyroid function in a patient presenting with obesity. Measurement of thyroid-stimulating hormone (TSH) will detect significant primary disease of the thyroid, but for rare secondary hypothyroidism, additional measurement of free thyroxine levels is needed (Chap. 395). Weight gain can also be a presenting feature of Cushing’s syndrome. Clinically, the presence of spontaneous bruising, livid striae, myopathy, and marked centripetal distribution of body fat helps to distinguish true endogenous hyper cortisolism from common obesity. This condition is usually reasonably straightforward to diagnose based on tests that approximate cortisol production rates (24-h urine free cortisol) or the suppression of serum cortisol by dexamethasone (Chap. 398). Occasionally, in patients with severe obesity, effects of adiposity on glucocorticoid metabolism can make it difficult to interpret results, and more sophisticated tests, including those measuring diurnal rhythm of cortisol, may be neces sary to establish or exclude the diagnosis with confidence. Weight gain can also be a presenting feature of patients with insulinoma, driven largely by the need to eat more frequently than normal to avoid hypoglycemia. Hypothalamic Damage The hypothalamic regions that control energy balance can be disrupted by tumors (such as craniopharyngio mas), inflammatory masses, or after a severe head injury (Chap. 391). In such cases, there is often some accompanying evidence of disruption of the hormonal functions of the anterior or posterior pituitary, although it may be subtle and the history of hyperphagia and weight gain is often short. It is worth noting that in common obesity, GH levels in response

Dementia Stroke Sleep apnea Hypertension Hypertriglyceridemia Ischemic heart disease Heart failure Gallstones Esophagitis Cancer of esophagus, colon, endometrium, pancreas, kidney Type 2 diabetes NAFLD PART 12 Endocrinology and Metabolism PCOS Arthritis Gout FIGURE 413-4 Obesity-related complications. The expanded fat mass that characterizes obesity predisposes to certain obesity-related complications (e.g., osteoarthritis of knees, reflux esophagitis, and obstructive sleep apnea) directly through its mass and/or volume. However, in the case of the metabolic, endocrine, and cardiovascular complications, the link is less clear. Further research is needed to establish whether some features of the expanded fat mass influence the development of these complications or whether other aspects of the chronically overnourished state, such as excess fat outside the fat depot, are more relevant. NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovarian syndrome. to provocative testing may be somewhat lower than normal, but this does not necessarily suggest the presence of a structural lesion. ■ ■ADVERSE CONSEQUENCES OF OBESITY Mechanistic Considerations Obesity is associated with a wide range of pathologies that can adversely impact morbidity and mortality (Chap. 420). Some of these consequences are related, at least in part, to the direct mechani cal or gravitational effects of the expanded fat mass itself (Fig. 413-4). However, the principal mechanisms behind many of the complica tions of obesity are less likely to be due to the expanded fat mass itself but more closely related to the chronic state of overnutrition itself and its effects on tissues throughout the body. Adipose tissue Inflammation As people develop obesity, one of the first and most prominent biochemical abnormalities that develops is the need for increased circulating concentrations of insulin to maintain glucose homeostasis. This state of insulin resistance generally worsens with a greater degree of obe sity, but there is a high degree of interindividual variability. It is more prominent when fat is distributed more centrally. Insulin resistance/ hyperinsulinemia is likely to play a major role in the predisposition to metabolic endocrine and cardiovascular diseases seen more frequently in obesity and may even play a role in the predispo sition of people with obesity to develop certain cancers. FIGURE 413-5 How does obesity cause metabolic disease? Insulin resistance is one of the earliest complications of obesity and underlies and precedes many of its adverse health consequences. The disposal and production of glucose by the most important tissues, muscle and liver, respectively, become less sensitive to insulin, and this results in a compensatory increase in insulin secretion from the pancreas. There are two main theories for the association of obesity with insulin resistance. In the first, products of macrophages and other inflammatory cells that are more abundant in obese adipose tissue can, through paracrine or endocrine routes, disturb insulin’s action in muscle and liver cells. In the second, as adipose storage deposits fill up, they become less able to take on excessive calories, which end up being stored as ectopic lipid in tissues such as muscle and liver, which are not primarily designed to store nutrients of this type. The evidence in humans is stronger for the latter hypothesis. The main sites of insulin action in the body are the liver and skeletal muscle. Thus, for insulin resistance to be discernible at the level

of the whole body, the action of insulin must be disturbed in one or both of these tissues. It seems unlikely that an expanded fat cell mass would do that directly. How then does obesity lead to a state of insulin resistance? One hypothesis suggests a leading role for the inflammation that occurs in the adipose tissue in obesity (Fig. 413-5). This undoubt edly happens, as there are more macrophages in obese than nonobese adipose tissues, and this is associated with higher levels of inflamma tory markers in the circulation of people with obesity. The majority of macrophages in obese adipose tissue are found in clusters around dead or dying adipocytes, so it appears that these cells are clearing debris after cell death. Studies in animal models provide strong support for the notion that this inflammatory state is mechanistically linked to insulin resistance, but evidence

from humans for this is not as strong. An alternative hypothesis is that as individuals develop obesity they become less able to safely store nutrients in their adipose tissue and begin to redirect macronutrients to other tissues that are not designed for fat storage and may be damaged by the nutrient excess. This cer tainly happens to people who are born with a lack of adipose tissue (lipodystrophy) who, early in life, develop severe versions of all the metabolic complications that are seen in obesity as they have no safe depot in which to store excess nutrients. There are stronger human data from both genetic and pharmacologic studies for the existence of the latter mechanism. How ectopic fat leads to insulin resistance and other damaging effects is still a puzzle, but it is very likely a major driver of pathology associated with obesity. Metabolic Complications • DYSLIPIDEMIA The insulin resis tance of obesity is frequently associated with dyslipidemia character ized by high circulating triglycerides and low high-density lipoprotein cholesterol (Chap. 419). Occasionally, the hypertriglyceridemia may be severe enough to put the patient at risk of pancreatitis. Although there is a relationship between obesity and raised circulating levels of low-density lipoprotein cholesterol (which is the major risk factor for coronary artery disease), genetic factors independent of obesity and the type of dietary fat consumed probably have an even greater impact. Chronic imbalance of energy intake > Energy expenditure Expansion of adipose tissue depots Limited fat cell capacity for continuing storage Inflammatory cytokines Storage of lipid in nonadipose tissue Defective glucose handling in liver and muscle Insulin resistance/compensatory hyperinsulinemia

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