The Physiology of Body Weight Regulation: Relevance to the Etiology of Obesity in Children

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ABSTRACT. The prevalence of obesity in children and adults in the United States has increased by more than 30% over the past decade. Recent studies of the physiology and molecular genetics of obesity in humans have provided evidence that body weight (fat) is regulated. Some of the genes encoding the molecular components of this regulatory system have been isolated from rodents. The increasing prevalence of obesity in the United States apparently represents the interaction of these genes with an environment that encourages a sedentary lifestyle and consumption of calories. The rapid increase in the prevalence of obesity emphasizes the role of environmental factors, because genetic changes could not occur at this rate. Thus, understanding of the relevant genes and how their effects are mediated by environment and development should lead to more effective prophylaxis and therapy of obesity. Although no clear environmental factors have been identified as causative of obesity, the rapid increase in the prevalence of obesity and the seeming voluntary immutability of adult body fatness can be taken as tacit evidence that the pediatric environment can be altered in a way that affects adult body weight. Pediatrics 1998;101:525–539; obesity, genetics, energy metabolism, body weight regulation.

ABBREVIATIONS. NHANES, National Health and Nutrition Examination Surveys; C/EBP, CCAAT-enhancer binding protein; BMI, body mass index; CNS, central nervous system; ASIP, agouti signaling protein; MCH, melanin-concentrating hormone; VMH, ventromedial hypothalamus; LH, lateral hypothalamus; NPY, neuropeptide Y; PVN, paraventricular nucleus.

Storage of excess calories as fat must ultimately result from a net positive energy balance (energy intake greater than energy expenditure) over time. Thus, the physiologic determinants of body composition are 1) energy intake, 2) energy output, and 3) partitioning of energy stores as fat, carbohydrate, and protein. Many physiologic systems (endocrine, gastrointestinal, central nervous, peripheral nervous, and cardiovascular) affect these functions. Small changes in any of these determinants can, over time, result in substantial changes in body weight.
Given the importance of energy stores to individual survival and reproductive capacity, the ability to conserve energy as adipose tissue would have conferred survival advantage in the environment in which hominids evolved. For this reason, humans are presumably enriched for genes that promote energy intake and storage and that minimize energy expenditure. By virtue of their effects on fat stores, such genes would also enhance female fertility and the ability to breastfeed offspring. However, in the modern industrial environment that provides easy access to calorically dense foods and encourages a sedentary lifestyle, the metabolic consequences of these genes are maladaptive.

In the 10 years between the National Health and Nutrition Examination Survey II (NHANES II, a survey that included measures of body fatness in the United States between 1976 and 1980) and NHANES III (the same survey repeated between 1988 and 1991), the prevalence of overweight, based on body mass index (BMI; kg/m²) corrected for age and sex in earlier national surveys (Nutrition Health and Examination Survey [NHES] II [1964 to 1965] and NHES III [1966 to 1970]) has increased by ≈40%. A similar increase in the prevalence of adult obesity (24% in NHANES II vs 33% in NHANES III) was reported over the same period. The observation that the prevalence of obesity increased substantially over a single decade, a period much too brief for any significant change to have occurred in the genetic makeup of the population of the United States, indicates that the current relative adiposity is a product of the interaction between genetic predisposition with regard to the storage of body fat and an environment (low physical activity, high availability of calorically dense foods) that is increasingly permissive to the expression of that genetic tendency. Although there are clearly strong genetic influences on susceptibility to obesity, large changes in the prevalence of obesity over such a short time must reflect major changes in nongenetic factors, providing tacit evidence that some instances or aspects of obesity must be responsive to, or preventable by, manipulation of the environment (eg, diet, physical activity).

Thus, obesity is a complex phenotype that resolves the influences of genes, development, and environment. In any individual—and in the same individual at different times of life—the relative influence of these factors may vary. In this sense, obesity is a prototype of many of the diseases (eg, hypertension, dyslipidemia, type II diabetes mellitus) now confronting medical science. Among the most important concepts about these phenotypes is the idea that relevant genes mediate susceptibility to disease in a specific environmental context and is not the inevitable occurrence of the disease regardless of the environment. Individuals with an otherwise potent genetic predisposition to obesity still will be lean in an environment of food deprivation or high demand for physical activity; individuals not genetically predisposed to obesity may still become so in an environment that includes tasty, calorically dense foods and few inducements to physical activity. Thus, in any effort to elucidate the genetic bases for susceptibility to obesity, the environment in which the obesity is occurring remains a critical factor with regard to what sorts of genes will be identified. Because the genes that mediate susceptibility to obesity may affect energy intake, energy expenditure, and partitioning of stored calories between lean tissues and fat, the ability to define the gross metabolic basis for obesity is very important for determining which genes are relevant to the phenotype. Current research regarding the molecular physiology of weight regulation is providing the reagents and physiologic targets that should permit the mechanistic description of specific instances of human obesity. In this article, we describe some of the insights provided by these studies. These insights will surely be relevant to the etiology of childhood obesity. Currently, however, the precise etiology of any specific instance of human obesity remains unknown. This statement is true for both the rare dysmorphic obesity (eg, Prader–Labhart–Willi Syndrome) and the garden variety obesity in the population at large.

**REVIEW**

**Biochemistry and Development of Adipose Tissue**

White adipose tissue derives from mesenchyme. Fully differentiated adipocytes are first detectable in the human fetus at ≈15 weeks of gestation. Both adipocyte volume and number continue to increase throughout gestation, with maximal rates of change achieved after approximately the 30th week. During the third trimester of pregnancy, there is an 12-fold increase in total body fat (percentage body fat increases from ≈5% to 15%). The composition of stored triglyceride is similar to that of maternal stores early in gestation, but fat stored during the third trimester consists predominantly of saturated fatty acids. These observations suggest that early gestational lipid stores reflect passive transfer of maternal fatty acids, whereas most newborn lipid stores are attributable to increased fetal intrahepatic lipogenesis from carbohydrate (preferential synthesis of saturated free fatty acids).

During the first year of extrauterine life, most adipose tissue growth occurs by enlargement (hypertrophy) rather than by increased numbers of adipocytes (hyperplasia), but after 2 years there is little additional increase in adipocyte volume in the nonobese child. The growth of adipose tissue and the changes in body composition with age are illustrated in the Figure. In nonobese children, there is no significant change in fat cell volume from 2 to 14 years of age and there is only a slight increase in fat cell number from 2 to 10 years of age. In obese children, there is continual enlargement of adipocytes without hyperplasia during the same period. These observations are consistent with a model of adipose tissue growth (see below) whereby adipocyte hyperplasia is triggered by achievement of a critical adipocyte volume.

As far as we know, there is a virtually unlimited pool of preadipocytes represented in the pericytes of the pericapillary endothelium. These preadipocytes are visually and biochemically indistinguishable
from other fibroblasts and have no detectable lipo-genic or lipolytic enzyme activity (see below). Once a cell differentiates into an adipocyte, the differentiation is irreversible (terminal differentiation). In vitro and in vivo studies suggest that there is local control of adipocyte differentiation, perhaps by signals generated from preadipocytes or mature adipocytes. When fibroblasts from the pericapillary epithelium are examined in tissue culture, they multiply until a state of confluence (the culture plate is completely covered with fibroblasts) is reached. Once confluence has occurred, isolated nests of cells differentiate terminally into groups of adipocytes separated by patches of undifferentiated cells. However, if a space is created around those undifferentiated cells, thereby stimulating them to divide further, they will also differentiate. In vivo, maximal adipocyte lipid content appears to be ~1 g of lipid per cell. Once this degree of hypertrophy has occurred, recruitment of new adipocytes begins, which suggests that adipocyte hypertrophy may generate a signal that encourages additional differentiation of preadipocytes. During therapeutic weight loss in children, the rate at which new fat cells develop is diminished. However, fat cell number apparently continues to increase at a rate significantly greater than that of age-matched controls on an ad libitum diet. These data imply that fat cell hyperplasia can be restrained therapeutically, but that the rate of appearance of new fat cells may, to some extent, be programmed genetically or developmentally.

Several transcription factors described recently have powerful effects on adipogenesis. PPARγ2 is a member of the peroxisome proliferator activated receptor subfamily of nuclear hormone receptors that is induced very early in adipocyte differentiation. PPARγ2 is a transcription factor that controls or induces adipocyte differentiation and expression of adipocyte-specific genes. Inducers of PPARγ2 expression include insulin and insulin-sensitizing compounds (eg, the thiazolidinediones), glucocorticoids, certain prostaglandins, and, as the name implies, peroxisome proliferating drugs such as clofibrate. PPARγ2 interacts in a cooperative manner with other transcription factors in adipogenesis. CCAAT-enhancer-binding protein α (C/EBPα) is a transcription factor expressed relatively late in adipogenesis. As with PPARγ2, C/EBPα activates adipocyte-specific genes such as the adipocyte P2 (aP2) gene, which promotes synthesis of an intracellular fatty acid-binding protein. Deficiency of PPARγ2 or C/EBPα, created by expressing them in cells that lack specific activators for one or both of them, results in significant declines in fat cell lipid content and adipogenesis, whereas cells (eg, myoblasts) that do not differentiate into adipocytes will undergo adipogenesis if expression of both of these factors is induced transgenically. The other C/EBPs, C/EBPβ and C/EBPγ, are expressed very early in adipogenesis. C/EBP appears to increase the expression of PPAR. Another important factor in adipocyte differentiation is the transcription factor adipocyte determination and differentiation-dependent factor 1 (ADD1/SREBP1), which is also expressed early in adipogenesis. This protein induces additional adipocyte differentiation as well as expression of PPAR, fatty acid synthetase, and lipoprotein lipase. It is conceivable that some of these proteins play a role in mediating the effects of adipocyte volume on recruitment and differentiation of new adipocytes. Certain of these transcription factors might be targeted for future preventative treatments in children who are genetically at risk for obesity.

Heritability of Obesity-related Phenotypes in Humans

There are rare instances of single gene disorders that result in human obesity (eg, Prader-Willi, Bardet-Biedl, Ahlstrom, Cohen), associated with other striking (dysmorphic) phenotypes. In most

Figure. Age-related changes in body composition of children.
humans, however, body fatness is a continuous quantitative trait reflecting the interaction of development and environment with genotype. Studies in twins, adoptees, and families indicate that as much as 80% of the variance in BMI is attributable to genetic factors. That is, the genetic influences on body weight are as potent as those on height. Heritability of adipose tissue distribution (intraabdominal versus subcutaneous fat), physical activity, resting metabolic rate, changes in energy expenditure that occur in response to overfeeding, certain aspects of feeding behavior, food preferences, lipoprotein lipase activity, maximal insulin-stimulated acylglyceride synthesis, and basal rates of lipolysis are estimated to be as high as 30% to 40%.

Segregation analyses in which the familiality of obesity is examined under various genetic models have found evidence for segregation of major genes (allele frequencies, 0.14 to 0.26) influencing BMI (20% to 35% of variation) in human populations. As might be expected, the heritability of early-onset obesity appears to be considerably higher than that for adult-onset obesity. What is likely to be inherited most strongly is the rank order of body fat relative to one's peers within a population sharing the same environment.

Animal Models of Genetic Obesity

Because it is so difficult to define or control the environment of humans experimentally, and because the attainment of an obese state may actually rectify the metabolic mechanisms (increased energy intake relative to expenditure or decreased energy expenditure relative to intake) that predispose an individual to obesity, animal models of obesity have been looked at intensively for clues to the relevant genes in humans. Rodent mutations in which obesity is inherited as a simple Mendelian recessive or dominant to obesity, animal models of obesity have been used. For human genes, all capital letters indicate homologues in rodents; all of these mutations are in genes for metabolic factors. That is, the genetic influences on body weight appear to type II diabetes mellitus. Table 1 lists the extent, single gene mutations that result in obesity in rodents; all of these mutations are in genes for which human homologues exist.

These rodent mutations themselves exemplify phenotypically different subgroups of obesity that could have homologues in humans. For example, hyperinsulinemia is more pronounced in Lep and Lep<sup>db</sup> than in <i>tub</i> or <i>Yellow</i> (A<sup>y</sup>). Similar to that in humans, body fat distribution varies among these rodent mutations. A<sup>y</sup>, <i>fat</i>, and <i>tub</i> show diffuse increases in body fat, whereas Lep<sup>db</sup> and Lep<sup>ob</sup> tend to deposit fat inguinally and axially. Partitioning of stored calories as fat, carbohydrate, and protein also is affected by these mutations. Compared with their nonobese littermates, Lep<sup>ob</sup> and Lep<sup>db</sup> mice have reduced fat-free mass despite their increased body weight.

The complexity and redundancy of the mechanisms affecting body fatness also are exemplified by these rodent models of obesity. Each mutation produces a distinct obese phenotype by interrupting different biochemical systems that regulate body weight. Lep<sup>db</sup> and Lep<sup>ob</sup> are mutations in a signaling system in which a protein (OB protein [leptin]) is secreted from adipocytes in proportion to fat mass (mutant in <i>ob</i>). The concentration of ambient leptin is sensed centrally by a receptor (OB receptor or leptin receptor, mutant in <i>Lep<sup>ob</sup></i> mice and <i>Lep<sup>db</sup></i> rats) with resultant central nervous system (CNS)-mediated changes in food intake and energy expenditure, including hyperphagia, defective nonshivering thermogenesis, and preferential partitioning of excess caloric storage as fat.

Yellow mutations in the agouti gene (A<sup>y</sup>, A<sup>vy</sup>, A<sup>sy</sup>, or A<sup>vy</sup>) result in obesity and increased linear growth, hyperphagia, hyperinsulinemia, hypercortisolism, and increased lipogenesis. These mutations result in ectopic overexpression of the agouti gene, which encodes agouti signaling protein (ASP). In mice, ASP normally is expressed only in hair follicles, where it competitively inhibits binding of melanocyte-stimu-

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**Table 1. Rodent Obesity Mutations**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation</th>
<th>Biochemical Effect of Mutation</th>
<th>Rodent</th>
<th>Human</th>
<th>Physiologic Effect of Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin (Lep)</td>
<td>&lt;i&gt;ob&lt;/i&gt;</td>
<td>Leptin deficiency</td>
<td>Mouse 6</td>
<td>7q31.3</td>
<td>Central effects → ↑ food intake and ↓ energy expenditure</td>
</tr>
<tr>
<td>Leptin receptor (Lep)</td>
<td>&lt;i&gt;Lep&lt;sup&gt;ob&lt;/sup&gt;&lt;/i&gt; or &lt;i&gt;Lep&lt;sup&gt;db&lt;/sup&gt;&lt;/i&gt;</td>
<td>Deranged leptin signal transduction</td>
<td>Mouse 4</td>
<td>1p31</td>
<td>Central effects → ↑ food intake and ↓ energy expenditure</td>
</tr>
<tr>
<td>Carboxypeptidase E (Cpe)</td>
<td>&lt;i&gt;fat&lt;/i&gt;</td>
<td>Deficiency of carboxypeptidase E</td>
<td>Mouse 8</td>
<td>4q32</td>
<td>Interferes with prohormone (including neuropeptide) processing and intracellular transport</td>
</tr>
<tr>
<td>Tubby (tub)</td>
<td>&lt;i&gt;tub&lt;/i&gt;</td>
<td>Deficiency of phosphodiesterase-like molecule</td>
<td>Mouse 7</td>
<td>11p15</td>
<td>Possible effects on cellular apoptosis in hypothalamus Blockade of melanocyte-stimulating hormone, and possibly other ligands at MC4R</td>
</tr>
<tr>
<td>Agouti&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&lt;i&gt;A&lt;sup&gt;y&lt;/sup&gt;&lt;/i&gt;</td>
<td>Ectopic (brain) overexpression of ASP</td>
<td>Mouse 2</td>
<td>20q11.2</td>
<td></td>
</tr>
</tbody>
</table>

Rodent obesity mutation symbols are based on current nomenclature. Earlier designations for Lep<sup>ob</sup> and Lep<sup>db</sup> were <i>ob</i> and <i>db</i>, respectively. With the exception of the dominant mutation in the agouti gene, all the mutations shown are recessive. For human genes, all capital letters are used.
lating hormone at the melanocortin-1 receptor, resulting in synthesis of pheomelanin (yellow pigment) rather than eumelanin (black pigment). When expressed centrally in the yellow mouse, ASP apparently competes with the normal ligand for the melanocortin-4 receptor. The melanocortinergic projections activated by melanocortin-4 receptor are believed to exert a tonic inhibition of feeding. Hence, disruption of this system by ASP results in hyperphagia.36

Fat is a mutation in a gene coding for an enzyme (carboxypeptidase E) that excises dibasic paired residues at the carboxyl terminus of peptide prohormones, including processing of insulin and neuropeptides such as neuropeptide Y, proopiomelanocortin, and melanin-concentrating hormone (MCH).37 Neuropeptide Y and MCH are hypothalamic neuropeptides that inhibit food intake,38 and the fat mutation may result in obesity because of an inability to synthesize these peptides fully. These animals have profound hyperinsulinemia, which progresses to moderate obesity by the time they are 8 weeks of age.39

Tub is a mutation in a phosphodiesterase-like gene that results in mild obesity with progressive hyperinsulinemia, loss of photoreceptors in the retina, and loss of inner ear hair cells, resulting in loss of vision and hearing. The tub gene product is highly expressed in the hypothalamus, and it has been hypothesized that a defect in this product may result in apoptosis of specific cells within the ventromedial hypothalamus (VMH), resulting in an obese phenotype similar to that observed when the VMH is ablated iatrogenically.7,32

Candidate Genes Regulating Body Fatness in Humans

Because obesity can arise only from an excess of energy intake over expenditure or the preferential partitioning of stored calories to fat, the search for candidate obesity genes should focus on those genes that play a role in these aspects of energy metabolism. This strategy is being used currently to examine extended human families, sib pairs, and individuals within populations for linkage or association of obesity and related phenotypes40 to molecular markers within populations for linkage or association of obesity and related phenotypes40 to molecular markers corresponding to candidate genes based on metabolic physiology (eg, β3-adrenoreceptor,41 glucocorticoid receptor,42 Na,K-ATPase43), human syndromic obesity,44 and rodent obesity genes (eg, Lep and Lepr in rodents, LEP and LEPR in humans).33 Tentative linkage to LEP has been reported in groups of extremely obese whites,45,46 but not in the Pima Indians, for whom obesity and diabetes are extremely common.47 In a Hispanic population, a locus near LEP appears to be linked to some measures of adiposity.48 A recent study identified a region on human chromosome 2 that accounted for 47% of the variation in serum leptin concentrations and 32% of the variation in fat mass in a population of Mexican-Americans.49 Linkage of obesity50 and noninsulin-dependent diabetes mellitus-related (acute insulin response)51 phenotypes to a region (1p22–p31) that contains LEPR (leptin receptor) has been reported. The fine genetic structures of all of these genes are known, enabling efforts to detect coding sequence variations in genomic DNA, which may play a role in human obesity.52

RESULTS

Regulation of Body Weight

The history of the scientific study of obesity began in 1773 with the demonstration by Lavoisier that the heat of a guinea pig was derived from chemical processes identical to those that occur in a piece of burning wood, thus demonstrating the chemical identity of combustion and respiration and shattering vitalistic views of biologic processes. In the ensuing 125 years, a distinguished succession of physicists, chemists, and physiologists established the principles of thermodynamics and their applicability to biological systems.53 Much of the struggle to understand the biology of weight regulation has been conducted in the presence of powerful, sometimes subtle, frequently commercially motivated, vitalist misconceptions or misrepresentations about bioenergetics and Western societal views of obesity as the psychological product of self-indulgence and overgratification instead of as a disease.54 Almost 50 years ago Mayer55,56 first proposed that the CNS sensed glucose and regulated energy intake by a glucostatic mechanism; Kennedy57 hypothesized a lipostatic system whereby body fat stores produced a signal that affected systems of energy homeostasis, and Meyer58 proposed an aminostatic system whereby the quality and quantity of amino acids ingested affected systems of energy homeostasis. More recently, we have amassed a substantial body of evidence that body weight is regulated59 by complex signaling systems that provide afferent signals (including glucostatic, lipostatic, and aminostatic signals) to the CNS about the nutritional state of the organism, which then are translated into efferent signals that affect energy intake and expenditure (see below).

Epidemiologic Evidence That Body Weight Is Regulated

Epidemiologic observations of the relative constancy of body composition over long periods of time support strongly a biological basis for the regulation of body fat. The relative stability of body weight over time in most individuals,60 despite wide variation in energy intake and expenditure, and the poor long-term results of weight reduction therapies (90% to 95% of adults and children who lose weight return to their previous state of fatness)61,62 suggest that attempts to maintain an altered body weight are opposed by systems of energy homeostasis that defend a highly individualized body weight or setpoint. If body weight were not regulated, then simply increasing caloric intake by 150 calories per day above weight maintenance calories per kilogram of usual body weight (the caloric content of one 8-oz glass of milk) would result in a yearly caloric excess of ∼55 000 kcal or a weight gain of ∼25 pounds. Yet, according to the Framingham study, the average adult gains only ∼20 pounds (∼40 000 kcal of stored energy versus ∼20 million calories ingested over the same period) between 35 and 55 years of age.60
Physiologic Evidence That Energy Expenditure Changes to Oppose Alterations in Body Weight

Energy Expenditure

Regulation of body weight in obese and never-obese adults differs only in that these individuals defend different body weights. Decreases in body weight of both obese and never-obese adults are resisted by equivalent declines in energy expenditure.63,64 A formerly obese individual requires 10% to 15% fewer calories to maintain a normal body weight than a never-obese individual of the same body composition.65,66 This decline in 24-hour energy expenditure primarily reflects a decrease in nonresting energy expenditure (energy expended in physical activity) and, to a lesser extent in some studies, resting energy expenditure (resting cardiorespiratory work and the maintenance of transmembrane ion gradients).64,66 Maintenance of an increased body weight is resisted with equal metabolic force. Thus, a lean or obese individual who has gained weight to 10% above usual body weight requires ~15% more calories to maintain an elevated body weight. The metabolic forces opposing the maintenance of an altered body weight are equally potent for obese and never-obese adults and oppose weight gain as strongly as they oppose weight loss. It also is notable that when weight-maintenance caloric requirements are normalized for body composition (ie, adjusted to account for the fact that it requires more calories to move a larger amount of weight), there are no significant differences in the metabolic requirements of lean and obese individuals to maintain their usual body weight. Thus, the view that obese adults suffer from a primary metabolic abnormality at their usual body weight is incorrect. However, a formerly obese individual requires substantially fewer calories to maintain body weight than a never-obese person of the same body weight and composition.64 Studies of adults during maintenance of a 10% reduced body weight have shown that the mechanical efficiency of skeletal muscle (calories expended per unit of work) is increased after weight loss. Conversely, during maintenance of a 10% increased body weight, the mechanical efficiency of skeletal muscle (calories expended per unit of work) is diminished.68 Adults who have maintained reduced body weight for several years continue to demonstrate the metabolic opposition to the maintenance of a reduced body weight.65 These studies suggest that weight alteration-associated long-lasting changes in metabolic efficiency constitute an important part of the mechanism by which systems of energy homeostasis in adults oppose the maintenance of an altered body weight.

As indicated previously, the increasing prevalence of obesity in the United States provides tacit evidence that an increase in the body weight an individual tends to maintain over time can be facilitated by environmental factors. Currently, there is no evidence, however, that environmental factors can be manipulated to lower the usual weight or setpoint that is maintained by an individual without invoking the metabolic opposition to the maintenance of a reduced body weight described above. A critical and unanswered question is whether the compensatory changes opposing the maintenance of an altered body weight that occur in adults also occur in children. If they do not, aggressive treatment of obesity early in childhood may be accompanied by permanent downward resetting of the regulatory systems controlling body weight.

Two systems in the body that are primary regulators of the efficiency with which energy is used are the autonomic nervous system and the thyroid axis. The parasympathetic limb of the autonomic nervous system includes the vagus nerve. Increased parasympathetic nervous system tone slows the heart rate and increases insulin release69–72 (ie, favors weight gain). Increased output from the sympathetic limb of the autonomic nervous system stimulates thyroid hormone release, increases heart rate, diminishes insulin release, and increases thermogenesis in brown adipose tissue69–72 (ie, favors weight loss). Thyroid hormone increases energy expenditure by increasing heart rate, blood pressure, and energy expenditure.73 Obese and never-obese adults studied at their usual body weight, during weight loss, and during maintenance of a reduced body weight demonstrate significant increases in parasympathetic nervous system activity and decreases in sympathetic nervous system activity and in circulating concentrations of thyroid hormone, compared with usual weight both during weight loss and during maintenance of a reduced body weight.75,76 The increases in parasympathetic nervous system activity and mechanical efficiency of skeletal muscle and the decreases in sympathetic nervous system activity and circulating concentrations of thyroid hormone during maintenance of a reduced body weight are consonant with the declines observed in resting and nonresting energy expenditure described previously.

An important question is whether an individual destined to become obese demonstrates increased metabolic efficiency before actually becoming obese. Many of the rodent genetic models of obesity discussed below demonstrate increased metabolic efficiency within the first few weeks of life before obesity occurs.31,32,77–79 Roberts et al80 examined resting metabolic rate and 24-hour energy expenditure in 3-month-old infants born to both lean and obese mothers. Twenty-four-hour energy expenditure was significantly lower at 3 months in those infants who were obese by the age of 1 year. The finding that 24-hour energy expenditure, but not resting metabolic rate, was significantly lower in infants destined to become obese suggests that the lower 24-hour energy expenditure is attributable to a decrease in the quantity of energy expended in physical activity. Similarly, low energy expenditure, adjusted for body composition, was associated with a fourfold increased risk of gaining more than 7.5 kg over 2 years in a study of adult Southwest Native Americans.
Weight reduction in some obese individuals may unmask the metabolic state that predisposed them to become obese. In this sense, the extra body fat of the obese may mediate (perhaps via a secreted protein such as leptin) a metabolic correction for low energy expenditure. However, other studies have not found that reduced energy expenditure was predictive of subsequent weight gain.

Energy Intake

Feeding behavior consists of decisions about initiation, composition, and termination of meals; these decisions are influenced by many internal and external factors. Prepubertal children allowed to consume food ad libitum over 6 days from a menu consisting of foods they liked showed wide variation in calories ingested per meal, but total daily energy intake was relatively constant, suggesting that, with presumably little knowledge of nutrition, children sense the number of calories they have consumed and tend to keep their caloric consumption relatively stable. It should be noted that energy intake must exceed energy output in the growing child. This excess of intake over output is especially pronounced during rapid growth periods in infancy and adolescence. In contrast, energy intake must equal output in the adult, whose body composition is constant. Theoretically, it may be possible to therapeutically exploit the differences in systems regulating energy homeostasis between children and adults so that an imposed degree of body fatness will be defended once growth ceases.

If changes in energy expenditure were the sole factor that opposed maintenance of a reduced body weight, then it would be relatively simple to prescribe a diet for life for the reduced-obese person. Simply staying on this diet would maintain the reduced weight. Many of the same hormones and areas of the brain that are involved in regulation of energy expenditure also influence feeding behavior (see below). For example, the leptin-deficient Lepr<sup>-/-</sup> mouse is both hypometabolic and hyperphagic. The observation that humans maintain a relatively constant body weight despite variations in caloric intake and physical activity implies that energy output and intake are tightly linked. However, the interlocking control mechanisms of these regulators of energy input and output remain incompletely understood.

Integration of Energy Intake and Expenditure

The ventromedial hypothalamus (VMH) and lateral hypothalamus (LH) have important effects on feeding behavior (energy intake) and autonomic regulation of energy expenditure. Lesions of the VMH render rats hyperinsulinemic, hyperphagic, and hypometabolic compared with their sham-operated littermates (ie, the lesioned animals behave similarly to an underfed rat). Once they have reached a certain level of increased adiposity (the degree of obesity they achieve is directly proportional to the size of the hypothalamic lesion), lesioned rats eat the same quantities of food as their lean sham-operated littermates and no longer gain weight at a comparatively excessive rate. The observation that these lesioned animals will consume excess calories and gain excess weight to achieve a certain degree of fatness and then will defend that degree of fatness by appropriate adjustments of food intake suggests that the VMH lesion may have altered a setpoint for body weight. Similarly, rats with lesions of the LH become hypermetabolic and hypophagic (ie, their energy expenditure and feeding behavior are analogous to those of a nonlesioned overfed rat and remain so only until they reach a new lower body weight). The VMH and LH areas are, therefore, viewed more accurately as suberving and integrating complex systems regulating both feeding behavior and energy expenditure. Evidence for the presence of similar regulatory centers in humans is provided by the observation that traumatic or infectious injury to the human hypothalamus results in a syndrome characterized by hyperphagia, hyperinsulinemia, and overactivity of the parasympathetic nervous system.

Molecular Mediators of Feeding Behavior and Energy Expenditure

There are many central and peripheral hormones and neurotransmitters that may act directly or indirectly on systems of energy homeostasis. Neuropeptide Y (NPY), a potent endogenous central appetite stimulant, is synthesized by cell bodies in the arcuate nucleus of the hypothalamus and transported axonally to the paraventricular nucleus (PVN), where the highest concentrations are found. NPY also is synthesized and released from the adrenal gland and sympathetic nerves, but peripherally synthesized NPY does not pass the blood–brain barrier. In rodents, food restriction is associated with a significant increase in production of hypothalamic NPY mRNA and intracerebroventricular administration of NPY is a strong stimulator of feeding behavior. In addition, injection of NPY into the rodent PVN increases adipose tissue lipoprotein lipase activity and decreases brown fat sympathetic nervous system activity and thermogenesis (ie, exerts coordinate effects on energy intake and output that favor weight gain). Despite the compelling evidence for the physiologic importance of NPY in energy homeostasis, a mouse with a genetically engineered knockout of the NPY gene has normal body fat and food intake and becomes normally hyperphagic with food restriction. This finding highlights the extraordinary redundancy of the physiologic systems regulating caloric storage.

The mixed α- and β-adrenergic agonists epinephrine and norepinephrine may act as both appetite stimulants (α-adrenergic) and suppressants (β-adrenergic). The net effects of these endogenous catecholamines are, therefore, dependent on the relative degree of expression of α- and β-adrenergic receptor subtypes in target tissues. Dopamine and serotonin act as appetite suppressants. The catecholaminergic and serotoninergic systems are exploited by current antiobesity medications, which act to decrease energy intake via the sympathetic nervous system (eg, phentermine), to decrease appetite by inhibiting...
serotonin reuptake (e.g., d-fenfluramine), or by affecting both catecholaminergic and serotoninergic systems (e.g., sibutramine).6

Various other peptides (corticotropin-releasing factor, galanin, glucagon-like peptide I, growth hormone-releasing hormone, cholecystokinin, glucagon, MCH) may modify the feeding behavior mediated from moment to moment by monoamines.7 The production and release of these neuropeptides, in turn, is probably influenced by humoral signals, which indicate the size of adipose tissue depots, e.g., insulin and leptin (see below).

Glucocorticoids play a permissive role in obesity. The increase in body fat associated with endogenous or exogenous glucocorticoid excess is well recognized.108 Surgical or pharmacologic adrenalectomy of genetically obese or VMH-lesioned animals ameliorates the obesity. These effects are attributable in part to secondary elevations in corticotropin-releasing factor, which reduces food intake and modulates the appetite-stimulating effects of NPY.110 Adrenalectomy also sensitizes rats to the anorexigenic effects of intracerebral insulin. Intracerebral injection of corticosterone potentiates the expression of NPY mRNA and the amount of hypothalamic NPY protein.110 Gonadal steroids also have potent effects on body weight. Administration of estradiol reduces food intake, partly by reciprocal effects on corticotropin-releasing factor (increase) and NPY (decrease) activity in the hypothalamus.111

Candidate Signals From Adipose Tissue

The relative long-term constancy of body weight has led many investigators to hypothesize the existence of adipose tissue-mediated signals to the brain that reflect the amount of calories stored. By centrally mediated effects on efferent signals that affect energy intake and expenditure, the strength of the adipocyte signal induces changes in energy homeostasis, which promote the return of the individual to the usual body weight. The central mechanism integrating energy balance is responsive to a large number of inputs, including psychosocial and hedonic factors, neurophysiologic signals, and concentrations of monoamines and neuropeptides within specific synapses in the hypothalamus (Tables 2 and 3).

Leptin, encoded by the LEP gene,112 is synthesized by and released from adipose tissue and is clearly a candidate for an afferent signal relating adipose tissue mass to central systems of energy homeostasis. Leptin concentration in plasma is directly proportional to fat mass in animals113 and humans.114 Leptin reduces food intake, increases energy expenditure, and reduces body fat in Lepob (leptin-deficient) mice when administered systemically or intracerebroventricularly.115–117 Similar effects (at higher doses) are found in nonobese animals.118 Hormones that affect leptin expression in adipose tissue include insulin (increase),119 glucocorticoids (increase),119 gonadal steroids (leptin concentrations in premenopausal fe-

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**TABLE 2.** Endogenous Chemicals Affecting Energy Intake and Expenditure: Appetite Stimulants

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Site of Action</th>
<th>Effect on Energy Intake</th>
<th>Effect on Energy Expenditure</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPY</td>
<td>PVN</td>
<td>The most potent endogenous stimulant of food intake identified; ↑ during food restriction</td>
<td>↑ Lipoprotein lipase activity; ↑ Sympathetic nervous system tone; ↑ thermogenesis after central administration104</td>
</tr>
<tr>
<td>Norepinephrine and epinephrine</td>
<td>PVN (α-effect)</td>
<td>α-Adrenergic stimulation stimulates food intake</td>
<td>↓ Lipolysis, ↓ heart rate (attributable to vasoconstriction), ↓ energy expenditure (?)108,174</td>
</tr>
<tr>
<td>Insulin</td>
<td>VMH, LH, liver, fat, muscle</td>
<td>Central administration → ↓ NPY and ↑ food intake275</td>
<td>↑ Acylglyceride synthesis, ↓ lipolysis; ↓ NPY → ↓ lipoprotein lipase activity, sympathetic tone and thermogenesis111</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td></td>
<td>↑ Food intake; ↑ expression of NPY mRNA and [NPY]; adrenalectomy decreases fat mass in rodents with genetic and surgical (VMH-lesioned) obesities; ↑ brain levels of norepinephrine and food intake stimulating effects of central norepinephrine are blocked by adrenalectomy108,110</td>
<td>↓ Thermogenesis, perhaps attributable to ↓ CRF synthesis108,109,111</td>
</tr>
<tr>
<td>Galanin</td>
<td>PVN</td>
<td>↑ Food intake and ↑ preference for fat intake, may depend on norepinephrine because central galanin administration → ↑ norepinephrine and galanin effect is blocked by α1-adrenergic antagonists76</td>
<td>↓ Circulating concentrations of insulin and corticosterone76</td>
</tr>
<tr>
<td>Opioids (dynorphins, endorphins, and enkephalin)</td>
<td></td>
<td>↑ Food intake after activation of μ or δ receptor is blocked by opiate antagonists76,177</td>
<td></td>
</tr>
<tr>
<td>Growth hormone-releasing hormone</td>
<td></td>
<td>↑ Appetite78</td>
<td></td>
</tr>
<tr>
<td>Somatostatin</td>
<td></td>
<td>↑ Food intake179</td>
<td></td>
</tr>
<tr>
<td>Polypeptide YY MCH</td>
<td>?</td>
<td>↑ Food intake176</td>
<td></td>
</tr>
<tr>
<td>Neotensin</td>
<td></td>
<td>↑ Food intake161</td>
<td></td>
</tr>
</tbody>
</table>

Leptin concentration in plasma is directly proportional to fat mass in animals113 and humans.114 Leptin reduces food intake, increases energy expenditure, and reduces body fat in Lepob (leptin-deficient) mice when administered systemically or intracerebroventricularly.115–117 Similar effects (at higher doses) are found in nonobese animals.118 Hormones that affect leptin expression in adipose tissue include insulin (increase),119 glucocorticoids (increase),119 gonadal steroids (leptin concentrations in premenopausal fe-

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TABLE 3. Endogenous Chemicals Affecting Energy Intake and Expenditure: Appetite Suppressants

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Site of Action</th>
<th>Effect on Energy Intake</th>
<th>Effect on Energy Expenditure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine and epinephrine</td>
<td>LH (β-effect)</td>
<td>β-Adrenergic stimulation is anorectic[108]</td>
<td>β-Adrenergic stimulation → ↑ sympathetic nervous system activity, ↑ [thyroid hormone], ↑ energy expenditure; ↑ lipolysis</td>
</tr>
<tr>
<td>Dopamine</td>
<td>LH</td>
<td>Anorectic[127]</td>
<td></td>
</tr>
<tr>
<td>Serotonin</td>
<td>VMH</td>
<td>Anorectic[108]</td>
<td></td>
</tr>
<tr>
<td>Leptin</td>
<td>VMH Arcuate nucleus</td>
<td>Food intake in Lepb2 mice[114,116]</td>
<td></td>
</tr>
<tr>
<td>Cholecystokinin (CCK)</td>
<td>Vagus nerve, which projects to the PVN (type A receptor) and brain (type B receptor)</td>
<td>Anorectic effect of peripherally administered CCK is blocked by abdominal vagotomy; centrally administered CCK also has anorectic effect, perhaps by interaction with adrenergic receptors[108,182]</td>
<td>↑ Sympathetic nervous system output; ↑ thermogenesis; ↑ energy expenditure</td>
</tr>
<tr>
<td>Corticotropin-releasing factor (CRF)</td>
<td>PVN</td>
<td>Anorectic (?), perhaps by effects on corticotropin or glucocorticoid production (see below); ↓ [CRF] in hypothalamus of Lepb2 rats[183]</td>
<td>May → ↓ energy expenditure because humans given glucagon intramuscularly gain weight despite decreasing caloric intake[185]</td>
</tr>
<tr>
<td>Uroctin</td>
<td>PVN</td>
<td>Anorectic, perhaps via mechanisms similar to CRF[184]</td>
<td></td>
</tr>
<tr>
<td>Glucagon</td>
<td>Vagus nerve, which projects to the PVN</td>
<td>Anorectic effect of peripherally administered glucagon is blocked by abdominal vagotomy[186]</td>
<td></td>
</tr>
<tr>
<td>Glucagon-like peptide-1 (GLP-1)</td>
<td>Hypothalamus</td>
<td>Anorectic, may transduce the anorectic signal from leptin; central administration of GLP-1 antagonist → ↑ feeding in response to NPY[108]</td>
<td></td>
</tr>
<tr>
<td>γ-Aminobutyric acid</td>
<td>VMH</td>
<td>Anorectic[108]</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>VMH, LH, liver, fat, muscle</td>
<td>Anorectic[107-108]</td>
<td></td>
</tr>
</tbody>
</table>

It is clear that these systems are complex and redundant. Central mechanisms regulating energy intake and expenditure are affected by many afferent signals from the gastrointestinal, endocrine, and CNS and peripheral nervous system as well as adipose tissue. It is thus unlikely that a pharmacologic agent acting on any single afferent limb in this system (eg, catecholaminergic or serotoninergic agonists) will result in prolonged maintenance of a reduced body weight because other limbs of this body weight regulatory system will still actively oppose maintenance of the reduced weight.
Possible Environmental Influences on the Development of Obesity in Childhood

Etiology of Obesity in Children

Conclusions and Strategies for Research Into the Etiology of Obesity in Children

DISCUSSION

氤氲的文墨中，可能是一片苔藓的绿意，或者是一处枯枝的痕迹。

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pounds) versus adults of the same age who had been more macrosomic as infants (birth weight >9.5 pounds).140

Postnatal Influences

In 1968, Knittle and Hirsch141 reported that underfeeding or overfeeding of preweaning rat pups was associated with respective decreases or increases in body size, epididymal fat pad cell number, and cell size, which persisted despite subsequent ad libitum feeding of rat chow. The subsequent demonstration that obesity in humans may reflect adipocyte hyperplasia as well as hypertrophy, and demonstration of the apparent persistence of fat cells despite weight loss,142 suggested that early nutritional factors might influence later adiposity in humans. Currently, however, there is no firm evidence that early infant-feeding practices significantly affect risk of later obesity. Although formula-fed infants tend to be longer and heavier than their breastfed peers, these differences do not persist.143,144 Neither the age at which specific foods are introduced into the diet145-147 nor the relative amount of fat, carbohydrate, or protein in the diet131,148,149 exerts a significant influence on subsequent adiposity.

In the United States, obesity is most prevalent among children raised in urban communities and in smaller families. The prevalence of obesity also varies by ethnic group, geographic region, and socioeconomic class.150-153 Davies et al154 noted significant negative correlations between physical activity and body fatness in preschool children and concluded that low levels of physical activity in this age group were associated with increased body fat. Dietz and Gortmaker155 analyzed data obtained in NHES II (1963 to 1965, children 6 to 11 years of age) and NHES III (1966 to 1970, children 12 to 17 years of age) and noted that adiposity and the amount of time spent watching television in adolescence were significantly correlated, even when corrected for a history of obesity. They concluded that television-watching encourages inactivity and the consumption of calorically dense foods. Berkowitz et al156 noted that neonatal fatness and physical activity were not significantly correlated with parental adiposity or adiposity of the same children at the age of 4 to 8 years. The degree of adiposity in 4- to 8-year-olds was significantly positively correlated with parental adiposity and inversely correlated with daytime activity levels of the 4- to 8-year-olds. However, it is unclear whether inactivity and television-viewing in children cause obesity or whether obese children are less physically active because of social stigmatization by their peers or other secondary factors.

DISCUSSION

Conclusions and Strategies for Research Into the Etiology of Obesity in Children

Obesity in adults is associated with increased risk of a wide variety of medical morbidities. Genetic and physiologic data support the view that body fatness is inherited and that attempts to alter body weight therapeutically are opposed by changes in energy

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metabolism. The striking increase in the prevalence of obesity in the United States over the past few decades clearly indicates that body weights are defended in this manner, and that the effect of genetic influences on these body weights can be modified by environmental factors that favor positive caloric balance.

These observations support the common-sense idea that environment has a powerful effect on body fatness. It is not known, however, whether an individual’s intrinsic regulatory processes for control of body fatness can be altered permanently by early environmental manipulation. Animal data suggest that it may be possible to modify obesity risk in individuals through early interventions. Identification of the child who is at risk for obesity by use of historical (family history), clinical (current adiposity and growth pattern), genetic (allelic variations in specific genes), biochemical (eg, leptin), and metabolic (eg, low energy expenditure) markers; identification of environmental factors that increase the expression of this tendency toward obesity; and developmental stages at which the environment can be altered to prevent expression of such a tendency should be primary goals of future research.

Despite the fact that inheritance of most obesity in humans is complex, the problem is tractable when appropriate genetic strategies are used. Genetic mapping is a process used to relate a specific phenotype to a limited region of the genome and ultimately to a single gene. Once a phenotype is mapped accurately, the region can be searched for known genes, or the gene can be cloned by examining directly all DNA in the interval. This powerful strategy is most successful when the phenotype is unequivocal (affected vs unaffected, as for Huntington’s disease) and attributable to the effects of a single, fully penetrant gene (phenotype always present when mutation is present). The existence of phenocopies (similar phenotype not attributable to the gene) and multigenic traits (same phenotype attributable to different genes) can make it difficult or impossible to make such a map and—except in instances of extreme affection status (eg, BMI >50) or an isolated population group (Pimans, Samoans)—obesity is not likely attributable to variation in a single gene. Thus, for purposes of genetic analysis, the phenotype should be refined to isolate specific aspects of physiology for which interindividual differences are accounted for differences in the amount of body fat.

In addition to identifying a robust, distinct, physiologically relevant phenotype, it is necessary to have a map of high resolution with which to relate (map) the phenotype. Ideally, the map should be composed of molecular markers that are likely to differ between any two individuals. Such a requirement is fulfilled by the existence of dense (marker every 500 000 base pairs) maps of the human and mouse genomes. With such dense genetic maps, it has become possible to dissect a complex genetic disorder by so-called multipoint interval mapping of such quantitative trait loci. Recent experiments on seizure susceptibility and susceptibility to diet-induced obesity in mice and hypertension and non-insulin-dependent diabetes mellitus in rats suggest that even complex quantitative traits can be resolved to relatively few genetic loci if those loci exert major effects on phenotype.

On the basis of considerations raised earlier, it is clear that obesity can arise only from an excess of energy intake over expenditure. Thus, the search for candidate genes that might account for a genetic predisposition to obesity should be focused on those that play a role in energy intake or expenditure. This strategy is currently being used to examine extended human families, sib pairs, and individuals within populations for linkage of obesity and related phenotypes to molecular markers corresponding to candidate genes based on metabolic physiology (eg, beta-adrenoreceptor, glucocorticoid receptor, and rodent obesity genes (eg, Lep, Lepr)).

Another approach to the identification of genes related to the obese phenotype is to scan (for linked genetic intervals) the entire genome of individuals within families segregating for an obese phenotype. The feasibility of such an approach depends on the number of genes responsible for the phenotype in the individuals affected, the total number of relevant genes in the population, and the relative risk attributable to any locus. For disorders for which genetics clearly indicates a single gene with high penetrance, this approach is a reasonable means of identifying the region of the genome where the responsible gene is located. However, most obesity in humans is probably oligogenic, with genetic heterogeneity as well as strong environmental influences on phenotypic expression. Thus, in an ethnically heterogeneous population, and allowing for the potent effects of age and environment on penetrance of the phenotype, such a genome scan (which might be successful in a genetically homogeneous population) would have low power to detect even relatively significant genes. An alternative approach is to identify candidate genes for which biochemical or physiologic effects are consistent with possible molecular–physiologic mechanisms for the obese phenotype (eg, feeding peptides such as NPY, cholecystokinin, glucagon-like peptide 1, MCH, galanin, and their cognate receptors; genes related to energy expenditure such as Na,K-ATPase and mitochondrial uncoupling protein). These genes then can be mapped relative to pertinent phenotypes or examined for variations in coding and regulatory sequences that correlate with these phenotypes.

CONCLUSION

The apparent increase in the fatness of adults and children over the past few decades implies and the lack of success in maintenance of a reduced body weight in reduced-obese individuals suggests that the degree of body fatness an individual defends metabolically may be altered by early environmental influences. Additional identification of systems that oppose maintenance of an altered body weight, the age at which these systems become operant, and the environmental cues that affect the regulatory set-point of these systems may identify an optimal age at...
which therapy could be instituted to prevent a child who is genetically at risk of becoming obese from expressing that genetic tendency.

ACKNOWLEDGMENT

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Development of Eating Behaviors Among Children and Adolescents

Leann L. Birch, PhD, and Jennifer O. Fisher, PhD

ABSTRACT. The prevalence of obesity among children is high and is increasing. We know that obesity runs in families, with children of obese parents at greater risk of developing obesity than children of thin parents. Research on genetic factors in obesity has provided us with estimates of the proportion of the variance in a population accounted for by genetic factors. However, this research does not provide information regarding individual development. To design effective preventive interventions, research is needed to delineate how genetics and environmental factors interact in the etiology of childhood obesity. Addressing this question is especially challenging because parents provide both genes and environment for children.

An enormous amount of learning about food and eating occurs during the transition from the exclusive milk diet of infancy to the omnivore’s diet consumed by early childhood. This early learning is constrained by children’s genetic predispositions, which include the unlearned preference for sweet tastes, salty tastes, and the rejection of sour and bitter tastes. Children also are predisposed to reject new foods and to learn associations between foods’ flavors and the postigestive consequences of eating. Evidence suggests that children can respond to the energy density of the diet and that although intake at individual meals is erratic, 24-hour energy intake is relatively well regulated. There are individual differences in the regulation of energy intake as early as the preschool period. These individual differences in self-regulation are associated with differences in child-feeding practices and with children’s adiposity. This suggests that child-feeding practices have the potential to affect children’s energy balance via altering patterns of intake. Initial evidence indicates that imposition of stringent parental controls can potentiate preferences for high-fat, energy-dense foods, limit children’s acceptance of a variety of foods, and disrupt children’s regulation of energy intake by altering children’s responsiveness to internal cues of hunger and satiety. This can occur when well-intended but concerned parents assume acceptance of a variety of foods, and disrupt children’s regulation of energy intake by altering children’s responsiveness to internal cues of hunger and satiety. This can occur when well-intended but concerned parents assume how much to eat and when parents impose child-feeding practices that provide children with few opportunities for self-control. Implications of these findings for preventive interventions are discussed.

ABBREVIATION. BMI, body mass index.

This article addresses behavioral factors that influence food preferences, food intake, and energy regulation in children. Currently, the prevalence of childhood overweight is high and has increased dramatically since the 1970s.1,2 This increased prevalence is of concern because overweight children are at increased risk for social stigmatization, adult obesity, and chronic disease. Obesity shows familial aggregation; the risk of obesity among children of two obese parents is much higher than for children in families in which neither parent is obese.3 Familial aggregation has focused research attention on genetic factors in obesity,4 but the rapid secular increase in the prevalence of obesity cannot be attributable to genetic factors. The interaction of genes and environment influences phenotypes for intake and expenditure and suggests that a renewed focus on the family environment may provide information about behavioral factors that contribute to familial aggregation of adiposity.

Between 30% and 50% of the variance in adiposity within a population is attributable to genetic differences.5 However, these heritability estimates describe populations, not individuals, and do not provide information about the ways genetics and environment interact during development to produce childhood obesity. In the case of childhood obesity, the question is especially complex because 1) genes and environments also tend to be correlated—parents typically provide children with both genetics and environment; and 2) genetic factors can include behavioral predispositions that affect food intake and expenditure.6 A more complete understanding of what may characterize obesigenic environments

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The Physiology of Body Weight Regulation: Relevance to the Etiology of Obesity in Children
Michael Rosenbaum and Rudolph L. Leibel

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