8 Control of Weight: How Do We Get Fat?

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Keypoints

- Positive energy balance is the essential ingredient required to store body fat and become overweight.
- It is what the energy balance concept does not tell us that is important; for example, it does not explain genetic factors, gender differences in fatness, or effects of age or medications.
- An epidemiologic model for developing overweight in response to the environment identified food, reductions in energy expenditure, viruses, toxins, and drugs as contributing mechanisms.
- Cost of food has an important role in food choices.
- A homeostatic model for control of food intake and energy expenditure helps isolate the specific mechanisms that can be targeted for understanding and treating the problem.

Introduction

Research over the past two decades has provided an unprecedented expansion of our knowledge about the physiologic and molecular mechanisms regulating body weight and body fat [1]. One great step was the cloning of genes corresponding to five types of obesity in experimental animals that were due to single genes – so-called monogenic obesity syndromes – and the ensuing characterization of the human counterparts to these syndromes [2,3]. Subsequent research has added a number of other genes with lesser effects to the list of genes modifying obesity [4]. Extensive molecular and reverse genetic studies (mouse knockouts) have helped to identify critical pathways regulating body fat and food intake, and have validated or refuted the importance of previously identified pathways [2].

This chapter reviews this rapidly expanding literature from two perspectives. The first is an epidemiologic approach, considering environmental agents that affect the human being. The second views body weight regulation from a "set-point" or homeostatic approach by considering the way in which one part of the metabolic system communicates with another and how this system may be "overridden" by hedonic or pleasure centers.

Textbook of Diabetes, 4th edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Genetic factors

The epidemic of overweight is occurring on a genetic background that does not change as fast as the epidemic has been exploding. It is nonetheless clear that genetic factors have an important role in its development [2,4]. One analogy for the role of genes in overweight is that "genes load the gun and a permissive or toxic environment pulls the trigger."

Identification of genetic factors involved in the development of obesity increases yearly. From the time of the early twin and adoption studies more than 10 years ago [2], the focus has been on evaluating large groups of individuals for genetic defects related to the development of overweight [3,4]. These genetic factors can be divided into two groups: the rare genes that produce excess body fat and a group of more common genes that underlie susceptibility to becoming overweight – the so-called 'susceptibility' genes [2,4]. The field of genetic factors has been given a recent boost from genome-wide association studies, in which variants in large populations of tens of thousands of people are examined [4]. Using this genome-wide association strategy, 17 genes are now known that account for a small fraction of the variance in human body weight [5]. The most important of these is the FTO gene, which accounts for half of this effect. All of these genes are thought to affect the regulation of food intake.

Underlying the following discussion is the reality that genetic responses to the environment differ between individuals and affect the magnitude of the weight changes. Several genes have such potent effects that they produce overweight in almost any

environment where food is available. Leptin deficiency is one of them [3]. Most other genes that affect the way body weight and body fat vary under different environmental influences have only a small effect. That these small differences exist and differ between individuals accounts for much of the variability in the response to diet that we see.

Epigenetic and intrauterine imprinting

Over the past decade it has become clear that infants who are small for their age are at higher risk for metabolic diseases later in life. This idea was originally proposed by Professor David Barker and is often called the Barker or Developmental Origins of Health and Disease hypothesis [6]. Several examples illustrate its role in human obesity. The first was the Dutch winter famine of 1944, in which the calories available to the residents of the city of Amsterdam were severely reduced by the Nazi occupation [7]. During this famine, intrauterine exposure occurred during all parts of the pregnancy; caloric restriction during the first trimester increased the subsequent risk of overweight in the offspring [7].

Two other examples that fall into the category of fetal imprinting are the increased risk of obesity in offspring of mothers with diabetes [8] and in the offspring of mothers who smoked during the individual's intrauterine period [9,10]. In a study of infants born to Pima Indian women before and after the onset of maternal diabetes, Dabelea *et al.* [8] noted that the infants born after diabetes developed were heavier than those born to the same mother before diabetes developed [11,12]. The risk for overweight at age 3 years was predicted by smoking at first prenatal visit with an odds ratio (OR) of 2.16 (95% confidence interval [CI] 1.05–4.47). Despite being smaller at birth, these infants more than caught up by age 3 years [11,12].

Smoking during pregnancy increases the risk of overweight at entry to school from just under 10% to over 15% if smoking continued throughout pregnancy and to nearly 15% if it was discontinued after the first trimester, indicating that most of the effect is in the early part of pregnancy [13,14].

Environmental agents and overweight: an epidemiologic approach

One way to view the etiology of increased body fat is from the epidemiologic or environmental perspective. Food, medications, viruses, toxins and sedentary lifestyle can each act on the host to produce increased fatness. We need to remember, however, that for each of these agents there are genetic components.

Food is an environmental agent for obesity

We obtain all of our energy from the foods we eat and the beverages we drink. Thus, without food there could be no life, let alone excess stores of fat. The cost of this food is an important determinant of food choices. In addition to cost and total quantity, food styles of eating and specific food components may be important in determining whether or not we become fat.

Costs of food

Economic factors may have an etiologic role in explaining the basis for the intake of a small number of "excess calories" over time that leads to overweight [1]. What we consume is influenced by the price we have to pay for it. In the recent past, particularly since the beginning of the 1970s, the prices of foods that are high in energy density (fat and sugar-rich) have fallen relative to other items. The Consumer Price Index rose by 3.8% per year from 1980 to 2000 [15] compared with the rise in food prices, which rose by 3.4% per year. In the period 1960–1980, when there was only a small increase in the prevalence of overweight, food prices rose at a rate of 5.5% per year – slightly faster than the Consumer Price Index, which grew at a rate of 5.3% per year. The relative prices of foods high in sugar and fat have decreased since the early 1980s compared with those of fruits and vegetables. By comparison, Finkelstein *et al.* [15] note that between 1985 and 2000, the prices of fresh fruits and vegetables rose 118%, fish 77% and dairy 56%, compared with sugar and sweets, which rose only 46%, fats and oils 35% and carbonated beverages only 20%. Is it any wonder that people with limited income eat more sugar and fat-containing foods?

Quantity of food eaten

Eating more food energy over time than we need for our daily energy requirements produces extra fat. In the current epidemic the increase in body weight is on average 0.5–1 kg/year. The amount of net energy storage required by an adult to produce 1 kg of added body weight, 75% of which is fat, can be calculated by using a few assumptions. One kilogram of adipose tissue contains about 7000 kcal (29.4 mJ) of energy. If the efficiency of energy storage were 50%, with the other 50% being used by the synthetic and storage processes, we would need to ingest 14 000 kcal (58.8 mJ) of food energy. As there are 365 days in the year this would be an extra 20 kcal/day (40 kcal/day × 365 day/year = 14 600 kcal) [16]. For simplicity we can round this to 50 kcal/day or the equivalent of 10 teaspoons of sugar.

Has the intake of energy increased? The energy intake (kcal/day) was relatively stable during the first 80 years of the 20th century. During the last 20 years, however, there was a clear rise from about 2300 kcal/day to about 2600 kcal/day, or an increase of 300 kcal/day. This is more than enough to account for the 50 kcal/day net (100 kcal gross) required to produce the 1 kg weight gain each year [17].

Portion size

Portion sizes have dramatically increased in the past 40 years [18] and now need reduction. One consequence of the larger portion sizes is more food and more calories [17]. The US Department of Agriculture (USDA) estimates that between 1984 and 1994 daily calorie intake increased by 340 kcal/day or 14.7%. Refined grains provided 6.2% of this increase, fats and oils 3.4%, but fruits

and vegetables only 1.4% and meats and dairy products only 0.3%. Calorically sweetened beverages that contain 10% high-fructose corn syrup (HFCS) are made from these grain products. These beverages are available in containers of 12, 20 or 32 oz, which provide 150, 250 or 400 kcal if all is consumed. Many foods list the calories per serving, but the package often contains more than one serving. In 1954, the burger served by Burger King weighed 2.8 oz and had 202 kcal. By 2004, the size had grown to 4.3 oz and 310 kcal. In 1955, McDonald's served French fries weighing 2.4 oz and having 210 kcal. By 2004, this had increased to 7 oz and 610 kcal. Popcorn served at movie theaters has grown from 3 cups containing 174 kcal in 1950 to 21 cups with 1700 kcal in 2004 [19]. Nielsen & Popkin [18] have examined the portion sizes consumed by Americans and have shown the increased energy intake associated with the larger portions of essentially all items examined. Guidance for intake of beverages suggests intake of more water, tea, coffee and low-fat dairy products with lesser consumption of beverages that contain primarily water and caloric sweeteners [20]. The importance of drinking water as an alternative to consuming calories is suggested in a recent study. There was an inverse relationship between water intake expressed per unit of food and beverage intake and total energy intake. When the water intake was less than 20 g/gram of food + beverages, energy intake was 2485 kcal/day. At the highest quartile, when water intake was at or above 90 g/gram of food + beverage, energy intake had fallen to 1791 kcal/day. Thus, drinking water may be one strategy for lowering overall energy intake [21].

Energy density

Energy density interacts with portion size to affect how much is eaten. Energy density refers to the amount of energy in a given weight of food (kcal/g). Energy density of foods is increased by dehydrating them or by adding fat. Conversely, lower energy density is produced by adding water or removing fat. When energy density of meals was varied and all meals were provided for 2 days, the participants ate the same amount of food, but as a result obtained more energy when the foods were higher in energy density. In this experiment, they obtained about 30% less energy when the meals had low rather than high energy density [22,23]. When energy density and portion size were varied, Kral *et al.* [24] showed that both factors influence the amount that is eaten. The meals with low energy density and small portion sizes provided the fewest calories (398 kcal vs 620 kcal) [24].

Styles of eating

Breastfeeding is a case in which the style of eating can be associated with later weight gain. In infants, breast milk is their first food, and for many infants their sole food for several months. There are now a number of studies showing that breastfeeding for more than 3 months significantly reduces the risk of being overweight at entry into school and in adolescence when compared with infants who are breastfed for less than 3 months [25]. This may be an example of "infant imprinting" [26,27].

Restaurants and fast-food establishments

Eating outside the home has increased significantly over the past 30 years. There are now more fast-food restaurants (277 208) than churches in the USA [28]. The number of fast-food restaurants has risen since 1980 from 1 per 2000 people to 1 per 1000 Americans. Of the 206 meals per capita eaten out in 2002, fast-food restaurants served 74% of them. Other important figures are that Americans spent $100 billion on fast food in 2001, compared to $6 billion in 1970. An average of three orders of French-fried potatoes are ordered per person per week, and French-fried potatoes have become the most widely consumed vegetable. More than 100 000 new food products were introduced between 1990 and 1998. Eating outside the home has become easier over the last four decades as the number of restaurants has increased, and the percent of meals eaten outside the home reflects this. In 1962, less than 10% of meals were eaten outside the home. By 1992 this had risen to nearly 35%, where it has remained. In a telephone survey of body mass index (BMI) in relation to proximity to fast-food restaurants in Minnesota, however, Jeffrey *et al.* [29] found that eating at a fast-food restaurant was associated with having children, with eating a high-fat diet and having a high BMI, but not with proximity to the restaurant.

Eating in a fast-food restaurant also changes the foods consumed [30,31]. Paeratakul *et al.* [30] compared a day in which individuals ate at a fast-food restaurant with a day when they did not. On the day when food was eaten in the fast-food restaurant, less cereal, milk and vegetables were consumed, but more soft drinks and French-fried potatoes were eaten. Similar findings were reported by Bowman *et al.* [31], who reported in addition that on any given day, over 30% of the total sample group consumed fast food. In this national survey, several other features were also associated with eating at fast-food restaurants, including being male, having a higher household income and residing in the US South. Children who ate at fast-food restaurants consumed more energy, more fat and added sugars, and more sweetened beverages than children who did not eat at fast-food restaurants.

Night-eating syndrome

The original description of the night-eating syndrome was published in a classic paper by Stunkard in 1955 and updated recently [32]. Recent studies have refined this syndrome. It consists of individuals who eat more than 50% of their daily energy intake during the nighttime [1].

Frequency of food intake

Frequency of eating may increase the risk of obesity. Crawley & Summerbell [33] showed that among males, but not females, the number of meal-eating events per day was inversely related to BMI. Males with a BMI of 20–25 ate just over 6 times per day compared to less than 6 times for those with a BMI >25 kg/m^2.

Eating breakfast is associated with eating more frequently, and there are data showing that eating breakfast is associated with lower body weight. Eating breakfast cereal has been related to

decreased BMI in adolescent girls. Using longitudinal data on adolescent girls, Barton *et al.* [34] showed that as cereal intake per week increased from 0 to 3 times per week, there was a small, but significant, decrease in BMI.

Calorically sweetened soft drinks

One of the consequences of the lower farm prices in the 1970s was a drop in the price of corn, which made inexpensive the production of corn starch which is converted to HFCS. With the development of the isomerase technology in the late 1960s which could convert starch into the highly sweet molecule, fructose, manufacture of soft drinks entered a new era [35]. From the early 1970s through the mid-1990s, HFCS gradually replaced sugar in many manufactured products, and almost entirely replaced sugar in soft drinks manufactured in the USA. In addition to being cheap, HFCS is very sweet. We have argued that this "sweetness" in liquid form is one factor driving the consumption of increased calories which are needed to fuel the current epidemic of obesity.

The relationship of soft-drink consumption to calorie intake, to body weight and to the intake of other dietary components has been examined in both cross-sectional and longitudinal studies [36]. Of the 11 cross-sectional studies examining the relation of caloric intake and soft-drink consumption, nine found a moderately positive association. Among the four longitudinal studies, the strength of the association was slightly stronger. The authors conclude that when humans consume soft drinks there is little caloric compensation. That is, the soft drinks are "added" calories and do not lower the intake of energy in other forms. The strengths of these relationships were stronger in women and in adults. Not surprisingly, they found that studies funded by the food industry had weaker associations than those funded by independent sources.

Several studies on the consumption of calorically sweetened beverages in relation to the epidemic of overweight have received significant attention [35]. Ludwig *et al.* [37] reported that the intake of soft drinks was a predictor of initial BMI in children in the Planet Health Study. They went on to show that higher soft-drink consumption also predicted the increase in BMI during nearly 2 years of follow-up. Those with the highest soft-drink consumption at baseline had the highest increase in BMI. In one of the few randomized well-controlled intervention studies, Danish investigators [38] showed that individuals consuming calorically sweetened beverages during 10 weeks gained weight, whereas subjects drinking the same amount of artificially sweetened beverages lost weight. Equally important, drinking sugar-sweetened beverages was associated with a small, but significant, increase in blood pressure. Women in the Nurses' Health Study [39] also showed that changes in the consumption of soft drinks predicted changes in body weight over several years of follow-up. In children, a study focusing on reducing intake of "fizzy" drinks and replacing them with water showed slower weight gain than for those not advised to reduce the intake of fizzy drinks [40].

Fructose consumption, either in beverages or food, may have an additional detrimental effect. It has been linked to the development of cardiometabolic risk factors and the metabolic syndrome in participants in the Framingham Study [41]. Cross-sectionally, individuals consuming ≥1 soft drink per day had a higher prevalence of the metabolic syndrome (OR 1.48; 95% CI 1.30–1.69) and an increased risk of developing the metabolic syndrome over 4 years of follow-up. It may also increase the risk of gout [42] and diabetes [43].

Dietary fat

Dietary fat is another component of the diet that may be important in the current obesity epidemic [44–46]. In epidemiologic studies, dietary fat intake is related to the fraction of the population that is overweight [45]. In an 8-year follow-up of the Nurses' Health Study, Field *et al.* [47] found a weak overall association of percent fat and a stronger effect of animal fat, saturated fat and *trans* fat on fatness. In experimental animals, high-fat diets generally produce fat storage. In humans, the relationship of dietary fat to the development of overweight is controversial. It is certainly clear that ingesting too many calories is essential for the increase in body fat. Because the storage capacity for carbohydrate is very limited, it must be oxidized first. Thus, when people overeat, they oxidize carbohydrate and store fat. When fat is a large component of a diet, the foods tend to be "energy dense" and thus overconsumption is easy to achieve.

Low levels of physical activity

Epidemiologic data show that low levels of physical activity and watching more television predict higher body weight [48]. Recent studies suggest that individuals in US cities where they had to walk more than people in other cities tended to weigh less [49]. Low levels of physical activity also increase the risk of early mortality [50]. Using normal weight, physically active women as the comparison group, Hu *et al.* [51] found that the relative risk of mortality increased from 1.00 to 1.55 (55%) in inactive lean women compared with active lean ones, to 1.92 in active overweight women, and to 2.42 in women who are overweight and physically inactive. It is thus better to be thin than fat and to be physically active rather than inactive.

Television has been one culprit blamed for the reduced levels of physical activity, particularly in children. The first suggestion that TV viewing was associated with overweight was published by Gortmaker and Dietz. Using data from the National Health Examination Survey [52] and the National Longitudinal Study of Youth [53], they found a linear gradient from 11–12% overweight in children watching 0–2 hours/day to over 20–30% when watching more than 5 hours/day. Since that time a number of studies have shown that in both children and adults, those who watch TV more are more overweight. By one estimate about 100 kcal of extra food energy is ingested for each hour of TV viewing. In studies focusing on reducing sedentary activity, which largely means decreasing TV viewing, there was a significant decrease in energy intake with increased activity [54]. In the Early

Childhood Longitudinal Study, investigators found that between kindergarten and third grade, children watching more TV (OR 1.02) and eating fewer family meals together (OR 1.08) predicted a modest increase in weight [55].

Effect of sleep time and environmental light

Sleep time declines from an average of 14.2 ± 1.9 (mean ± SD) hours/day in infancy (11.0 ± 1.1 hours/day by 1 year of age) to 8.1 ± 0.8 hours/day at 16 years of age [56]. Sleep time declined across the cohorts from 1974 to 1993 due largely to later bedtime, but similar arising time. Nine epidemiologic studies have been published that relate shortness of sleep time with overweight. Six of these studies are cross-sectional in design, and three are longitudinal. The earliest of these studies was only published in 1992, but most were published after 2002. They include both children and adults. In a small case–control study involving 327 short-sleepers compared with 704 controls, Locard *et al.* [57] found that short-sleepers were heavier than the controls.

In two large cross-sectional studies in children, Sekine *et al.* [58] and von Kries *et al.* [59] found that there was a dose-dependent relationship between the amount of sleep and the weight of children when they entered school. Von Kries *et al.* [59] studied 6862 children aged 5–6 years whose sleeping time was reported in 1999–2000 by the parent, and followed-up in 2001–2002. Overweight in this study was defined as a weight for height greater than the 97th percentile. Children with reported sleeping time of less than 10 hours had a prevalence of overweight of 5.4% (95% CI 4.1–7.0), those who slept 10.5–11.0 hours per night had a prevalence of 2.8% (95% CI 2.3–3.3) and those who slept more than 11.5 hours had a prevalence of overweight of 2.1% (95% CI 1.5–2.9). Among the 8274 children from the Toyama Birth Cohort in Japan [58], there was a graded increase in the risk of overweight, defined as a BMI above 25 kg/m^2, as sleep time decreased. If the children who were reported to sleep more than 10 hours at age 3 had an OR of 1.0, those who slept 9–10 hours had an OR of 1.49, those with 8–9 hours sleep an OR of 1.89, and those children who were reported to sleep less than 8 hours had an OR for overweight of 2.87.

Another setting in which lighting has a role in the development of weight gain is seasonal affective depressive syndrome (SADS). For some people, the shortening of the daylight hours with the onset of winter is associated with depression and weight gain. When the days begin to lengthen in the spring this symptom complex is reversed. Current evidence suggests that it is related to changing activity of the serotonin system and can be treated with exposure to light or by manipulating brain levels of serotonin pharmacologically.

Medications that produce weight gain

Several drugs can cause weight gain, including a variety of hormones and psychoactive agents [1,60]. The degree of weight gain is generally less than 10 kg and not sufficient to cause substantial overweight. These drugs may also increase the risk of future type 2 diabetes mellitus.

Toxins

Smoking

The rise of smoking from 1900 to 1970 and its decline during the last 30 years of the 20th century has been tracked by the Centers for Disease Control. Weight gain after stopping smoking is gender-dependent, with men gaining an average of 3.8 kg and women 2.8 kg [61]. In a more recent analysis, men were found to gain 4.4 kg and women 5.0 kg [62] and it was calculated that this gain could account for about one-quarter to one-sixth of the increased prevalence of overweight. Several factors predict the weight gain, including younger age, lower socioeconomic status, heavier smoking and genetic factors [63]. Economists have calculated that a 10% increase in the price of cigarettes could increase BMI by 0.0251 kg/m^2 as a result of the decrease in smoking [64]. Snacks are the major component of food intake that rises when people stop smoking.

Organochlorines

In human beings, we know that body fat stores many "toxic" chemicals and that they are mobilized with weight loss. Backman first showed in 1970s that organochlorines in the body decreased after bariatric surgery. The metabolic rate can be reduced by organochlorine molecules [65], and conceivably prolonged exposure to many chlorinated chemicals in our environment has affected metabolic pathways and energy metabolism. Under these conditions, thyroid hormone synthesis is decreased, plasma T3 and T4 are decreased, thyroid hormone clearance is increased, and mitochondrial oxidation is reduced in skeletal muscle.

Monosodium glutamate

Food additives are another class of chemicals that are widely distributed and may be involved in the current epidemic of overweight. In experimental animals, exposure during the neonatal period to monosodium glutamate, a common flavoring ingredient in food, produces fatness [66].

Viruses as environmental agents

Several viruses produce weight gain in animals and the possibility that they do this in human beings needs more study. (This subject is ably reviewed by Atkinson [67].) It has been known for many years that the injection of several viruses into the central nervous system could produce fatness in mice. The list of viruses now includes canine distemper virus, RAV-7 virus, Borna disease virus, scrapie virus, SMAM-1 virus and three adenoviruses (types 5, 24 and 36). These observations were generally assumed to be pathologic in nature and not relevant to overweight humans. However, the recent finding that antibodies to one of the adenoviruses (AM-36) appear in larger amounts in some overweight humans than in controls challenges this view. This viral syndrome, resulting from AM-36, can be replicated in the ferret, a non-human primate. The features of the syndrome are modest increase in weight and a low cholesterol concentration in the circulation. Further studies are needed to establish that a syndrome of weight loss associated with low concentrations of

cholesterol clearly exists in human beings. If so, this would enhance the value of the epidemiologic model.

Regulation of body fat as a problem of homeostatic energy regulation with a hedonic override

A defect in the way the body responds to feedback signals is another way to view the problem of overweight. Such a system has four parts. The control center in the brain is analogous to the thermostat in a heating system. It receives information about the state of the animal or human, transduces this information into neurochemical signals, and activates pathways that lead to or inhibit feeding and the search for food. The signals that the brain receives come from the environment through sense organs and from the body through neural, nutrient or hormonal signals. The response the brain makes includes both the activation and inhibition of motor systems and the modulation of the autonomic nervous system or hormonal control system. Outside of the brain is the so-called controlled system and, for the purpose of this discussion, includes the digestive tract, which ingests, digests and absorbs food; the metabolic systems in liver, muscle and kidney, which transform nutrients; and the adipose tissue, which both stores and releases fatty acids and acts as a secretory endocrine organ [1].

Digestion, metabolism and fat storage

The controlled system consists of the gastrointestinal tract, liver, muscles, fat tissues, cardiovascular–pulmonary–renal system and supporting bone tissue. The ingestion, digestion and absorption of food provide nutrients to the body and also provide signals from these nutrients to the vagus nerve, which provides the major neural control of gastrointestinal function, and from hormones released by the gastrointestinal tract. The nutrients that are absorbed can be metabolized to provide energy, or they can be stored as glycogen in liver, as protein in muscle or as fat in adipose tissue.

The largest part of the energy we expend each day is for "resting" metabolism, which includes the metabolism of food, the transport of sodium, potassium and other ions across cell membranes, repair of DNA, synthesis of protein, the beating of the heart and functioning of the brain, liver and kidneys. Energy expenditure is most strongly associated with fat-free body mass.

We conclude that day-to-day energy balance is either positive or negative. We do not achieve meal-to-meal or day-to-day energy balance. Rather, if we are to avoid weight gain, we must achieve this over a longer time interval.

If we are to maintain a stable body weight, the metabolic mix of carbohydrate, fat and protein that is oxidized by the body must equal the amounts of these nutrients taken in as food. That is, to maintain energy balance requires that the mix of foods we eat be completely metabolized or oxidized. The capacity for storage of carbohydrate as glycogen is very limited and the capacity to store protein is also restricted. Only the fat stores can readily expand to accommodate increasing levels of energy intake above those required for daily energy needs. Several studies now show that a high rate of carbohydrate oxidation, as measured by a high respiratory quotient, predicts future weight gain [68]. One explanation for this is that when carbohydrate oxidation is higher than the intake of carbohydrate, carbohydrate stores are depleted. To replace this carbohydrate, an individual must eat more carbohydrate or reduce the oxidation of carbohydrate by the body, because the body cannot convert fatty acids to carbohydrate and the conversion of amino acids to carbohydrate mobilizes important body proteins [69]. Obese individuals who have lost weight are less effective in increasing fat oxidation in the presence of a high-fat diet than normal weight individuals, and this may be one reason why they are so susceptible to regaining weight that has been lost.

Physical activity gradually declines with age. If we are to avoid becoming overweight as we age, we must gradually reduce our food intake or we must maintain a regular exercise program. A moderate level of exercise is beneficial in two ways. First, it reduces risk of cardiovascular disease and type 2 diabetes, and second, it facilitates the oxidation of fat in the diet [70]. Maintaining an exercise program, however, is difficult for many people, particularly as they get older.

The concept of "energy wasting" through uncoupling proteins is one of the expanding basic science aspects of obesity. The original uncoupling protein-1 (UCP1) found in brown fat has a well-established role in helping newborn infants maintain body temperature. Increased expression and/or activation of this protein uncouples oxidation from phosphorylation by enhancing a leak of protons from the inner mitochondrial space, resulting in the conversion of energy to heat without storing the energy in ATP molecules. The UCP1 molecule is important in human infants, but its importance in adults, because of the very low levels of brown fat (and hence UCP1 expression) in adult humans, has been questioned until recently [71]. This new evidence for active brown adipose tissue in adult humans comes from the use of sophisticated techniques combining glucose uptake in tissues (using the ^{18}fluoro-deoxy-glucose) measured by positron emission tomography and computed tomography. Deposits of brown adipose tissue were demonstrated in the supraclavicular region, along the cervical vertebrae and along thoracic vertebrae. This activity can be blocked by propranolol, a broad-based beta-adrenergic-blocking drug, indicating that this glucose uptake is under control of the sympathetic nervous system. Activity can also be modulated by environmental temperature, with higher temperatures eliminating the uptake and lower temperatures increasing the uptake of labeled glucose. Whether the activity of this tissue can be enhanced by continued stimulation remains to be demonstrated.

The fat cell

The fat cells in adipose tissue serve two major functions. First, they are the cells that store and release fatty acids ingested in the food we eat or synthesized in the liver or fat cell. Second, fat cells

are a major endocrine cell, secreting many important metabolic and hormonal molecules [1].

Before fat cells can undertake these functions, however, they must be converted from precursor mesenchymal cells to mature fat cells. *In vitro* studies have shown a two-stage process – proliferation followed by differentiation. The proliferative phase is initiated by hormonal stimulation with insulin and glucocorticoids. After the cells begin to grow they enter a state of differentiation where they acquire the genetic state of mature fat cells that can store fatty acids, break down triglycerides, and make and release the many hormones that characterize the mature fat cell. Most of the fatty acids that are stored in human fat cells are derived from the diet, although these cells maintain the capacity for *de novo* synthesis of fatty acids [72].

The discovery of leptin catapulted the fat cell into the arena of endocrine cells [73]. The finding of a peptide released from adipose tissue that acts at a distance has refocused interest in the fat cell from primarily a cell that stores fatty acids to a cell with endocrine and paracrine functions. In addition to leptin, the fat cell secretes a variety of peptides, including lipoprotein lipase, adipsin (complement D), complement C, adiponectin, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), angiotensinogen, bradykinin and resistin, in addition to other metabolites such as lactate, fatty acids, glycerol and prostacyclin formed from arachidonic acid. This important endocrine tissue has thus greatly expanded its role. Adiponectin and resistin are recent additions to the growing list.

Messages to the brain from the environment and from the body

The brain receives a continuous stream of information from both the external and internal environments that have a role in the control of feeding. The external information provided by sight, sound and smell are all distant signals for identifying food. Taste and texture of foods are proximate signals generated when food enters the mouth. The classic tastes are sweet, sour, bitter and salty as well as "umami," a fifth taste. In nature most "sweet" foods also have vitamins and minerals, because they come from fruits. Sour and particularly bitter foods often contain unwanted chemical compounds. The extreme example of this is "bait shyness" or "taste aversion," the property that some items have that produces a permanent rejection of future food with the same taste. This is a "hard-wired" response in the brain that overrides the usual "feedback" signals.

A taste for fats, specifically unsaturated fatty acids, may be a sixth taste. Receptors on the tongue can identify certain fatty acids. The discovery of taste and smell receptors for polyunsaturated fatty acids on the taste bud that involves a potassium rectifier channel offers an opening into modifying taste inputs into the food-intake system [74]. An important advance was showing that the CD-36 receptor, which binds fatty acids, is the receptor for these fatty acids. These receptors are located on the lingual papillae of the tongue. Mice that do not have the CD36 receptor do not prefer solutions enriched with long-chain fatty acids or a high-fat diet. These receptors are in close proximity to Ebner glands, a source of lingual lipase, which cleaves triglycerides into fatty acids that can activate the CD36 receptor. When this receptor is activated, there is a rise in pancreatic secretions and an increase in their content [75].

Several gastrointestinal peptides have been studied as potential regulators of food intake. Most of these peptides, including cholecystokinin, gastrin-releasing peptide, oxyntomodulin, neuromedin B and polypeptide YY3-36 [76] reduce food intake. Cholecystokinin (CCK) was the first peptide shown to reduce food intake in animals and humans alike [77]. Investigation of the growth hormone secretagogue receptor has led to the identification of a new gastrointestinal hormone involved with the control of feeding. This peptide, ghrelin, is produced in oxyntic cells of the gastric fundus. It is a 28 amino acid peptide with an n-octanoyl residue on the serine in the 3-position. It is encoded by a gene with the symbol GHRL (OMIM 506353, chromosome 3p26-p25), and is derived from a 117 amino acid precursor. It stimulates food intake and reduces energy expenditure by acting on NPY/Agrp neurons that in turn inhibit anorexigenic neuromodulators that function through melanocortin and MC4R and works in animals and human beings when given systemically or into the brain. The level is low in overweight people, suggesting that it may have a role in controlling appetite and weight gain [78–80].

Pancreatic peptides, including amylin, glucagon-like peptide-1 (GLP-1), and enterostatin, also modulate feeding. Amylin is produced in the beta cell of the pancreas along with insulin and is co-secreted. In experimental studies, amylin has been shown to reduce food intake by acting on the amylin (calcitonin-like gene product) receptor. The major locations for this receptor are in the hind-brain and hypothalamus [81]. Pramlintide is a commercial analog of amylin which is currently used to treat diabetes. Both glucagon and its 629 amino acid derivative, GLP-1, reduce food intake in animals and humans. GLP-1 works in the brain and after peripheral administration. Exenatide is a GLP-1-like peptide isolated from the salivary glands of the Gila monster. It has been approved for the treatment of diabetes.

Nutrients may also be afferent signals to reduce food intake. A dip in the circulating level of glucose precedes the onset of eating in more than 50% of the meals in animals and human beings [82]. When this dip is blocked, food intake is delayed. The pattern recognized by this dip is independent of the level from which the drop in glucose begins. The small drop in glucose continues even when food is not available. The dip follows a small rise in insulin, suggesting a relationship of these two signals [1,77].

The brain and food intake

The brain plays the central role as receiver, transducer and transmitter of information from the peripheral organs [83]. This control is accomplished through sensory organs and internal signals that are integrated through central neurotransmitters that in turn activate neural, hormonal and motor efferent pathways.

Function of the right prefrontal cortex (PFC) may be particularly important. Brain diseases that affect the PFC have suggested that this area is involved in cognitive processes relevant for food intake and physical activity, and dysfunction of this area may represent a central event in the etiology of human obesity [84]. Weight gain and overeating were common side effects of frontal leucotomy performed in the mid-1900s for psychosis. Damage to the right frontal lobe can cause the gourmand syndrome, a passion for eating and a specific preference for fine food. Hyperphagia correlates positively with right frontal atrophy and negatively with left frontal atrophy in degenerative dementia. Hypoperfusion of the right frontal lobe using single photon emission computed tomography (SPECT) can be demonstrated in overeating conditions such as Kleine–Levin syndrome. In contrast, hyperactivity of the right PFC can lead to anorexia-like symptoms.

Monoamines, such as norepinephrine, serotonin, dopamine and histamine, as well as certain amino acids and neuropeptides, are involved in the regulation of food intake. The serotonin system has been one of the most extensively studied of the monoamine pathways [1,77]. Its receptors modulate both the quantity of food eaten and macronutrient selection. Stimulation of the serotonin receptors in the paraventricular nucleus reduces fat intake with little or no effect on the intake of protein or carbohydrate. This reduction in fat intake is probably mediated through 5-HT_{2C} receptors, because its effect is attenuated in mice that cannot express the 5-HT_{2C} receptor.

Stimulation of α_1-noradrenergic receptors also reduces food intake [1,77]. Phenylpropanolamine is an agonist acting on this receptor that has a modest inhibition of food intake. Some of the antagonists to the α_1 receptors that are used to treat hypertension produce weight gain, indicating that this receptor is also clinically important.

Stimulation of α_2 receptors increases food intake in experimental animals, and a polymorphism in the α_{2a}-adrenoceptor has been associated with reduced metabolic rate in humans. The activation of β_2 receptors in the brain, however, reduces food intake. These receptors can be activated by agonist drugs (beta-blockers), by releasing norepinephrine in the vicinity of these receptors, or by blocking the reuptake of norepinephrine.

Histamine receptors can also modulate feeding. Stimulation of the H_1 receptor in the central nervous system reduces feeding. Experimentally this has been utilized by modulating the H_3 autoreceptor, which controls histamine release. When the autoreceptor is stimulated, histamine secretion is reduced and food intake increases. Blockade of this H_3 autoreceptor decreases food intake. The histamine system is important in control of feeding because drugs that modulate histamine receptors may produce weight gain.

In animals, seasonally variable dopamine transmission in the suprachiasmatic nucleus appears to drive the storage of food at the appropriate time of year in anticipation of hibernation or migration. Loss-of-function mutations in the D_2 receptor gene are associated with overweight in human beings, and dopamine antagonists can induce obesity in humans. One suggestion is that this is through modulation of nutrient partitioning, with obesity in humans or fat storage in migratory and hibernating species as the results [85].

The opioid receptors were the first group of peptide receptors shown to modulate feeding. They also modulate fat intake [86]. Both the mu and kappa opioid receptors can stimulate feeding. Stimulation of the mu-opioid receptors increases the intake of dietary fat in experimental animals. Corticotropin releasing hormone (CRH) and the closely related urocortin reduce food intake and body weight in experimental animals.

The endocannabinoid system is a most recent addition to the central controllers of feeding [87]. Tetrahydrocannbinol, isolated from the marijuana plant, stimulates food intake. Isolation of the cannabinoid receptor was followed by identification of two fatty acids, anandamide and 2-arachidonoylglycerol, which are endogenous ligands in the brain for this receptor. Infusion of anandamide or 2-arachidonoylglycerol into the brain stimulates food intake. The cannabinoid-1 (CB-1) receptor is a preganglionic receptor, meaning that its activation inhibits synaptic transmission. Antagonists to this receptor have been shown to reduce food intake and lead to weight loss. There is also a peripheral ligand, oleylethanolamide, which inhibits food intake.

The discovery of leptin in 1994 opened a new window on the control of food intake and body weight [1,77,88]. This peptide is produced primarily in adipose tissue, but can also be produced in the placenta and stomach. As a placental hormone it can be used as an indicator of trophoblastic activity in patients with trophoblastic tumors (hydatidiform moles or choriocarcinoma). Leptin is secreted into the circulation and acts on a number of tissues, with the brain being one of its most important targets. The response of leptin-deficient children to leptin indicates the critical role that this peptide has in the control of energy balance.

To act on leptin receptors in the brain, leptin must enter brain tissue, probably by transport across the blood–brain barrier [86]. Leptin acts on receptors in the arcuate nucleus near the base of the brain to regulate, in a reciprocal fashion, the production and release of at least four peptides. Leptin inhibits the production of neuropeptide Y (NPY) and agouti-related peptide (AGRP) while enhancing the production of pro-opiomelanocortin (POMC), the source of α-melanocyte stimulating hormone (α-MSH) and cocaine and amphetamine-related transcript (CART) [86]. NPY is one of the most potent stimulators of food intake. It produces these effects through interaction with either the Y-1 or the Y-5 receptor. Mice that do not make NPY have no disturbances (phenotype) in food intake or body weight.

AGRP is the second peptide that is co-secreted with NPY into the paraventricular nucleus (PVN). This peptide antagonizes the inhibitory effect of α-MSH on food intake. Animals that overexpress AGRP overeat because the inhibitory effects of α-MSH are blocked.

The third peptide of interest in the arcuate nucleus is POMC, which is the precursor for several peptides, including α-MSH. α-MSH acts on the melanocortin-3 and melanocortin-4 (MC4) receptors in the medial hypothalamus to reduce feeding. When

these receptors are knocked out by genetic engineering, the mice become grossly overweight. In recent human studies, genetic defects in the melanocortin receptors are associated with significant excess of body weight. Many genetic alterations have been identified in the MC4 receptor, some of which are in the coding region of the gene and others in the regulatory components [89]. Some of these genetic changes profoundly affect feeding, whereas others have little or no effect.

Another important peptide in the arcuate nucleus is CART. This peptide is co-localized with POMC and, like α-MSH, inhibits feeding. Antagonists to these peptides or drugs that prevent them from being degraded would make sense as potential treatment strategies.

Two other peptide systems with neurons located in the lateral hypothalamus in the brain have also been linked to the control of feeding. The first of these is melanin-concentrating hormone (MCH) [90]. This peptide increases food intake when injected into the ventricular system of the brain. It is found almost exclusively in the lateral hypothalamus. Animals that overexpress this peptide gain weight and animals that cannot produce this peptide are lean. These observations suggest an important physiologic function for MCH.

The second peptide is orexin A (also called hypocretin). This peptide was identified in a search of G-protein linked peptides that affect food intake. It increases food intake, but its effects are less robust than those described above. However, it does seem to have a role in sleep.

Another recent addition to the list of peptides involved in feeding is the arginine-phenylalanine-amide group (RFa). The first of these peptides to be isolated from a mollusk had only four amino acids. The structure of the RFa peptides is highly conserved, with nearly 80% homology between the frog, rat, cow and humans [91]. In mammals there are five genes and five receptors for these peptides. The 26 and 43 amino acid members of the RFa peptide family stimulate feeding in mammals and are the ligands for two orphan G-protein coupled receptors located in the lateral hypothalamus and the ventromedial nucleus. This family of peptides has been involved in feeding from early phylogetic times including *Caenorhabdis elegans*. Their role in human beings is not yet established.

Neural and hormonal control of metabolism

The motor system for acquisition of food and the endocrine and autonomic nervous systems provide the major information for control of the major efferent systems involved with acquiring food and regulating body fat stores. Among the endocrine controls are growth hormone, thyroid hormone, gonadal steroids (testosterone and estrogens), glucocorticoids and insulin.

During growth, growth hormone and thyroid hormone work together to increase the growth of the body. At puberty, gonadal steroids enter the picture and lead to shifts in the relationship of body fat to lean body mass in boys and girls. A distinctive role for growth hormone has been suggested from studies with transgenic mice overexpressing growth hormone in the central nervous system. These mice are hyperphagic and obese, and show increased expression of NPY and agouti-related protein as well as marked hyperinsulinemia and peripheral insulin resistance [92]. Testosterone increases lean mass relative to fat and reduces visceral fat. Estrogen has the opposite effect. Testosterone levels fall as human males grow older, and there is a corresponding increase in visceral and total body fat and a decrease in lean body mass in older men. This may be compounded by the decline in growth hormone that is also associated with an increase in fat relative to lean mass, particularly visceral fat.

One recent finding suggests that the activity of the enzyme 11-β-hydroxysteroid dehydrogenase type 1, which reversibly converts cortisone to cortisol, may be important in determining the quantity of visceral adipose tissue. Changes in this enzyme may contribute to the risk of women of developing more visceral fat after menopause. A high level of this enzyme keeps the quantity of cortisol in visceral fat high and provides a fertile ground for developing new fat cells.

The sympathetic nervous system is an important link between the brain and peripheral metabolism. It appears to be involved in the oscillation of fatty acids in visceral fat that accompanies the increased fat as dogs overeat a high-fat diet [93]. Using genetic homologous recombination (knockout) mice lacking the β1, β2 and β3 receptor have been produced. These animals show a normophagic obesity with cold intolerance. They have higher circulating levels of free fatty acids. Thus sympathetic nervous system function is essential to prevent obesity and to resist cold [94–96].

Conclusions

This chapter aims to provide a snapshot of our understanding of the regulatory systems for factors that are etiologic in obesity. Both epidemiologic and metabolic feedback models are reviewed in assembling this information. We have not reached the end of the story. It is clear, however, that we have a much better glimpse into its operation – one that can provide us a better framework for thinking about both the etiology of obesity and its possible treatments.

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