Food Intake, Metabolism, and Obesity in Humans

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INTRODUCTION

Energy Balance

Humans are continuous metabolizers but ingest food discontinuously. Although energy expenditure determines the energy requirement, energy intake is indirectly tuned to energy expenditure. When energy intake equals energy expenditure, body weight remains constant. Obviously, with an energy intake lower than energy expenditure one is in a negative energy balance, and with an energy intake higher than energy expenditure in a positive energy balance; and body weight decreases or increases, respectively. A persistent positive energy balance leads to obesity.

The first part of this review deals with the determinants of energy expenditure. The second part deals with tuning energy intake to energy requirement, as determined by energy expenditure. Special attention is paid to ‘‘obesity,’’ caused by a positive energy balance, and to ’body weight or energy balance regulation’ in children. Genetic factors and metabolic disturbances are included.

Energy Expenditure

Daily energy expenditure consists of four components, the sleeping metabolic rate (SMR), the energy cost of arousal, the thermic effect of food- or diet-induced energy expenditure (DEE: 10% to15%), and the energy cost of physical activity (AEE: 15% to 20%). Sometimes daily energy expenditure is divided into three components, taking SMR and the energy cost of arousal together as energy expenditure for maintenance or basal metabolic rate (BMR: 50% to 70%). BMR is usually the main component of average daily metabolic rate (ADMR) (1) (Fig. 1).

Energy Metabolism and Regulation of Energy Balance

Energy metabolism appears to be determined by body composition, i.e., fat-free mass and fat mass, implying body mass. Furthermore, gender, age, and physical
activity all determine energy metabolism, directly, or indirectly by determining body composition (1–3) (Fig. 2).

Gender Differences

Women and men show pronounced differences in energy metabolism. On average, women have a lower energy expenditure, mainly as a result of differences in body composition, compared with men. Additionally, hormonal and behavioral differences might play a role. Compared to men, women generally have less bone, fat-free and skeletal muscle mass, and a larger body fat content. Because gender differences mainly emerge during puberty, it is conceivable that sex steroid hormones are involved in determining gender-specific body composition.

Gender differences in energy metabolism may be the result of sexually dimorphic evolutionary pressures (4), i.e., differences in selection pressures because of sexual selection and differences in reproductive roles. In humans, where women do a large proportion of the initial caretaking of the offspring including pregnancy, selection has favored small female size with a relatively large energy store as an adaptation to starvation resistance. Women have possibly preferred large and active men to protect the offspring. The result is a gender difference in body size and body composition with important consequences for energy metabolism and in the maintenance of energy balance (1).

Sleeping or basal metabolic rate is usually compared between subjects by standardizing to an estimate of metabolic body size. Fat-free body mass, fat mass, age, and
gender are the predictors for SMR or BMR, but when these co-variates are included, gender does not come out as a significant contributor to the explained variation (1–3). Apparently SMR or BMR is not different for women and men when corrected for individual differences in body composition (3).

DEE in real life is assumed to be 10% to 15% of ADMR in subjects consuming an average mixed diet and being in energy balance. DEE can be measured over 24 hours in a respiration chamber. As expected, DEE is lower in women than in men. However, when DEE is expressed as a percentage of energy intake, the values for women and men are the same. Thus, DEE is comparable for women and men when adjusted for energy intake (5).

Activity-induced energy expenditure is the most variable component of ADMR. The doubly labeled water method provides quantitative estimates of AEE in daily life. Subsequently, however, there is no consensus on the way to normalize AEE for differences in body size. A frequently used method to quantify physical activity is by expressing ADMR as a multiple of BMR or SMR (6,7). It assumes that the variation in ADMR is due to body size and physical activity. The effect of body size on ADMR is corrected by expressing ADMR as a multiple of BMR or SMR; then, AEE is comparable for women and men (6,7).

With respect to gender differences in energy balance regulation, women and men appear to react differently to a disturbance of the energy balance. Women lose less weight when energy intake is restricted with a weight-reducing diet or when energy expenditure is increased with an exercise program. Also women probably do not lose much fat when they adopt a higher level of physical activity, as was shown

FIG. 2. Sleeping metabolic rate (SMR) plotted as a function of fat-free mass (FFM) for 37 subjects. Women: closed symbols; men: open symbols) with the calculated linear regression line (SMR [MJ/d] = 2.27 + 0.09FFM [kg], $r^2 = 0.8$) From Westerterp et al. (1).
from two meta-analyses on the relation between physical activity as derived from ADMR measured with doubly labeled water and body composition. In men, there was a significant inverse cross-sectional relationship between activity energy expenditure and percent body fat, whereas no such relationship was apparent in women (8–10). As another indication for a gender difference in energy regulation, women are more sensitive to changes in ambient temperature than men, again closely linked to gender differences in body size and body composition. The greater fat content, enhancing insulation, may not provide women with a thermoregulatory advantage over men. First, women generally have a smaller total body mass, resulting in a greater surface area per unit body mass. Second, a smaller lean body mass, the source of metabolic heat production, limits women's capacity for heat production, compared to men of comparable total body mass. Women show earlier signs of discomfort and an earlier increase in metabolic rate at a falling ambient temperature. At a rising ambient temperature, the thermal sensation and response with an increase in evaporative heat loss comes later in women, resulting in a narrower thermoneutral zone compared with men (11).

OBESITY

Role of Leptin in Fat Accumulation and Fat Distribution

Leptin, the product of the ob gene, is mainly produced by adipocytes and secreted into the circulation. This peptide may be an important metabolic signal between the adipose tissue and the hypothalamus (1). Leptin receptors have been shown to be less sensitive in the obese, who accumulate excess body fat, as a result of a positive energy balance (1). Together with sex steroid hormones, leptin is suggested to contribute to body fat distribution (1). Moreover, several studies have shown that leptin levels are reduced after exercise training and some studies have shown a gender-dependent effect of exercise training on serum leptin levels (12,13). The distribution of body fat is considered a secondary sex characteristic. Compared to men, premenopausal women have more subcutaneous body fat, with more and different sites of fat storage. In women, a larger proportion of body fat is localized in peripheral fat depots in breasts, hips, and thighs, while men tend to deposit fat in the abdominal regions (both subcutaneous and intra-abdominal or visceral fat depots) (1). The amount of fat in a certain depot is dependent on the number and size of adipocytes, the functional cells of the adipose tissue. The processes of fat storage and mobilization are dependent on energy balance, and modulated by several genetic, endocrine, and nutritional factors. Several decades ago, Jean Vague (14) was the first to notice the importance of the localization of body fat with respect to the increased health risks in obesity. Lower body obesity ('gynoid' obesity), typically seen in women, and upper body obesity ('android' obesity), most often present in men, were distinguished, based on anthropometric ratios. Android obesity or abdominal obesity was associated with an increased risk of cardiovascular diseases and non-insulin dependent diabetes mellitus, while these health risks were not commonly observed in the
female-type of obesity (14). Several studies have confirmed that the distribution of fat over the body is an important predictor of the metabolic disturbances in obesity, probably because of its specific localization in the abdominal cavity ("portal fat") combined with a higher turnover rate of visceral fat compared to subcutaneous fat (15). However, whether there is a causal relationship between visceral fat accumulation and metabolic disorders or whether visceral fat is just an epiphenomenon in the whole cluster of metabolic risk factors is still a matter of debate (16).

Men have larger visceral fat depots than premenopausal women (17), corrected for the amount of fat. Evidence is available to suggest that female sex hormones are involved in the preferential accumulation of subcutaneous fat in the typical 'female' body sites, which possibly serve an important function during pregnancy and lactation (1). It has even been suggested that female sex steroids are relatively protective against visceral fat accumulation because women can accumulate more body fat before reaching amounts of visceral fat that are similar to amounts in men (17). Observations in postmenopausal women are interesting in this respect because they suggest a shift toward a more male-type of fat distribution in this estrogen-deficient state, and prevention or at least minimization of this shift during hormone replacement therapy (1). Abdominal obesity, as assessed by the waist-to-hip ratio, is a common finding in women who are hyperandrogenic (with high levels of total testosterone or free testosterone and low levels of sex-hormone binding globulin) (18). Moreover, an accumulation of visceral fat with long-term testosterone administration to female subjects (female-to-male transsexuals) was increased (19,20). These findings in men and women are indicative of the complexity of the regulation of body fat distribution, and in particular of visceral fat accumulation.

Etiology of Obesity: Age and Energy Metabolism

As in adults, in children the determinants of body composition contribute to energy metabolism, thus the major correlates of resting energy expenditure are fat free mass, fat mass, and gender (21,22). Moreover, seasonal and geographical determinants have been shown, through their effects on physical activity related energy expenditure (23).

Some evidence suggests that a reduced energy expenditure may be involved in the etiology of childhood obesity (24,25), while other cross-sectional studies in prepubertal children do not support the concept that reduced energy expenditure may be related to obesity (21,26).

Degree of parental obesity was examined as a potential determinant for energy expenditure in pre-pubertal children (5.0 ± 0.9 years of age) of both lean and obese parents (27), showing no significant correlations between components of energy expenditure in children and body fat in mothers or fathers.

Genetic Background: Down Syndrome and Energy Expenditure

Other studies of the role of energy expenditure in the etiology of obesity have included studies in subjects with genetic conditions associated with obesity. For
example, the doubly labeled water method has been used to examine energy expenditure and requirements in children with Down syndrome, who have a high prevalence of obesity (28). No significant differences were found for total and non-resting energy expenditure.

Genetic Background: Prader-Willi Syndrome and Energy Expenditure

On the contrary, in a group of children with high susceptibility to the development of obesity, i.e., children with the Prader-Willi syndrome (PWS), a decreased energy metabolism has been found, in addition to an almost insatiable appetite (29,30). The pathophysiologic background of impaired metabolism as well as the main features of PWS is most likely based on dysfunction of various hypothalamic centers. Sleeping metabolic rate was 23%, and activity-related energy expenditure up to 38% lower in children with PWS than in obese controls (29,30). The low sleeping metabolic rate was explained by a low fat-free mass. Fat-free mass appeared to be reduced in relation to fat mass in this syndrome (29,30). The reduced growth of the fat-free tissues in children with PWS may well be related to an abnormality of the hypothalamic-pituitary-gonadal axis. Together with a possible functional growth hormone deficiency, the decreased levels of gonadotropins might take away the natural urge to be lively and playful (29,30).

Longitudinal Studies Related to the Development of Obesity

A major limitation for the majority of studies that have examined the role of energy expenditure in the etiology of obesity is their cross-sectional design. Because growth of individual components of body composition is likely to be a continuous process, longitudinal studies are needed to evaluate the rate of body fat change during the growing process. Therefore examinations were conducted to see whether childhood energy expenditure and body composition influenced the rate of change in body fat relative to fat-free mass over a 4-year period. The rate of change in fat mass adjusted for fat-free mass was 0.08 ± 0.64 kg/year (range, -1.45 to 2.22 kg/year). This was similar among children of two non-obese parents, children with one non-obese and one obese parent, but significantly higher in children with two obese parents (0.61 ± 0.87 kg/year). The major determinants of change in fat adjusted for fat-free mass were gender (greater relative fat gain in girls), initial fatness, and parental fatness (31). None of the components of energy expenditure were inversely related to change in fat adjusted for fat-free mass, indicating a genetic component in the development of body composition (31).

Pre-obese Models

Other "pre-obese" models that have been used to study the potential role of energy expenditure on the etiology of obesity include examination of ethnic groups at higher risk of obesity (e.g., Mohawk Indians and African Americans). In Mohawk
children in upstate New York, the prevalence of obesity is estimated as 44% (32). However, it was shown that total energy expenditure was actually 8.5% higher in Mohawk compared to white children living in Vermont, because of 37% higher physical activity–related energy expenditure in the Mohawk children (27). In African-American children, a 14% lower resting energy expenditure was found compared with white children, adjusting for age, gender, weight, fat-free mass, and fat mass (33). Among girls aged 6 to 16 years, lower resting energy expenditure was also found in African Americans than whites, adjusting for both body weight and lean body mass (34). In Birmingham Alabama, the prevalence of obesity in African-American children is almost twice that seen in white children (35). Energy expenditure components and body composition in healthy pre-pubertal white (17 girls, 22 boys) and African-American (29 girls and 30 boys) children (21) showed no significant effects of ethnicity on total energy expenditure, resting energy expenditure, or physical activity–related energy expenditure after adjusting for body composition.

SUMMARY OF THE ROLE OF ENERGY EXPENDITURE IN THE ETIOLOGY OF OBESITY

Collectively, the previous findings demonstrate that there are discrepant findings regarding the role of energy expenditure in the etiology of obesity in children. This could potentially be explained by a number of additional factors. For example, differences or changes in energy expenditure and/or energy intake could occur at distinct critical periods of development (such as in early infancy or adolescence), and may thus result in energy imbalance. In addition, there could be individual differences and susceptibility to the impact of altered energy expenditure on the regulation of energy balance as demonstrated in studies in which twins were challenged with underfeeding or overfeeding (36,37). Thus, the impact of energy expenditure on the etiology of obesity could vary among different subgroups of the population (e.g., boys vs girls, different ethnic groups) and could also have differential effect within individuals at different stages of development. It is conceivable that susceptible individuals fail to compensate for periodic fluctuations in energy expenditure. Also, although a 14-day measure of energy expenditure by doubly labeled water is considered a long-term measure, this period is actually quite short when compared to the time scale for the development of childhood obesity, which could also be a slow and gradual process. For example, comparing children of two obese parents versus children of two non-obese parents, the difference in the rate of change in fat mass relative to fat-free mass was less than 1 kg of fat per year, or less than 3 g of excess fat gain per day (31). This is equivalent to a continual daily energy imbalance of 0.11 MJ (about 2% of total daily energy flux). From a methods standpoint, even the most sophisticated of current techniques, would be unable to identify this energy imbalance as a “defect” in energy expenditure components (nor as excess in energy intake, relative to needs).
GENERAL IMPLICATIONS FOR THE PREVENTION OF OBESITY

Recent studies in children provide important information relating to targeting of obesity and health risk prevention programs. The increase in body weight in children (35) and its relation with increased disease risk early in life (38) and later in life (39) are likely to be most successfully addressed through population-based, public health prevention programs targeted at the critical stages of development. In girls, for example, there is a need to target prevention before puberty with an emphasis on increasing physical activity. Targeting a reduction in energy intake in isolation may compromise growth and necessary energy acquisition, and exacerbate the risk of introducing eating disorders. Physical activity has many benefits in children, including improvement in body weight (40), body composition (21), attainment of psychological well-being (41), and optimal bone health (42). A further advantage of promoting habitual physical activity implies proportionally less sedentary behavior, which is a major risk factor for obesity.

ENERGY BALANCE IN THE ELDERLY

Despite the long-term agreement between EI and EE, there is a tendency for a gradual increase in body weight with increasing age (21,43) (Fig. 3). This is the conclusion from cross-sectional measurements because longitudinal studies on body weight changes in individual subjects do not exist. One of the few long-term studies following individual body weights is the Framingham study (21,44). Cross-sectional data covering all adult age groups are available from life insurance companies, especially for men. These data show that the tendency for an increase in body weight is restricted to early adulthood. Figure 3 shows changes in body weight and body composition with age, as compiled by Forbes and Reina (44). Weight shows an initial increase with only small changes thereafter.

The constancy of body weight does not mean that the energy content of the body does not change as body composition changes with age. With increasing age, there is a systematic increase of the fat mass (FM) and a decrease of the fat-free mass (FFM) (21,43,44).

However, in terms of energy turnover, the change in the energy store is small. The average gain in FM of 15 kg, though in itself an impressive number, takes place over more than 50 years, or more than 18,250 days. Thus, the average daily fat gain is less than 1 g and, translated in energy using an energy equivalent of 38 kJ/g FM, about 30 kJ/day. At a daily energy turnover of 10 MJ, the average fat gain amounts only 0.3%, again showing how small effects can have large consequences.

It is impossible to prevent the ‘fattening’ of the body with increasing age. It is often suggested that people gain FM and lose FFM (muscle mass) because of a gradual decline of physical activity with age. Apart from a general trend for a slow increase in body weight, there are changes in relation to 'important life events,'
such as weight gain in women in relation to the number of pregnancies (Fig. 4) or after cessation of smoking (45,46).

**TREATMENT OF OBESITY**

With repeated treatment of morbid obesity, success decreases. This has been called the weight cycling effect, probably caused by the continuously decreasing basal metabolic rate. This only has been shown clearly in morbidly obese subjects during follow-up after vertical banded gastroplasty (47). The reduction in sleeping metabolic rate due to a lowered body weight was larger than expected based on the reduction in fat free mass. This suggests that the disproportional reduction in sleeping metabolic rate, even 12 months after vertical banded gastroplasty when weight loss was very mild, reflected the persistent metabolic susceptibility of the formerly morbidly obese subjects to weight regain. In studies in obese but not morbidly obese subjects
Physiologic Food Intake Regulation

Energy expenditure determines the energy requirement (1,21,49). In principle, energy intake is regulated physiologically by means of hunger and satiety (50,51).

With respect to food intake regulation in humans, in terms of meal size and meal frequency, two features are worth considering. First is the distinction between satiation and satiety. Satiation refers to the processes that bring a period of eating to an end; these processes influence the size of meals and snacks. Satiety refers to the inhibition of hunger and further eating that arises as a consequence of food ingestion, and determines inter-meal-interval, or meal-frequency (Fig. 5). These two kinds of processes therefore control events occurring during meals and between meals. The properties of food (and the act of ingesting it) trigger the initiation of the overlapping physiologic responses. The quantity and quality of the food will determine the intensity and time course of the biologic processes generated. This situation reflects the idea of the different satiating power of different types of food (50–55).

The biologic responses generated by food ingestion form part of a feedback circuit that influences the pattern of eating being displayed (51; see Fig. 5). This circuit can be seen as a network with three levels:

- psychological events (hunger, perception, cravings, and hedonic sensations) and behavioral operations (meals, snacks, energy, and macronutrient intakes)
• peripheral physiology and metabolic events
• neurotransmitter and metabolic interactions in the brain.

The expression of appetite reflects the synchronous operation of events and processes in the three levels. Neural events trigger and guide behavior, but each act of behavior involves a response in the peripheral physiologic system; in turn, these physiologic events are translated into brain neurochemical activity. This brain activity represents the strength of motivation and the willingness to refrain from feeding.

Viewed in this way, the psychobiologic system permits an understanding of the interrelationships among behavioral events that comprise eating, peripheral physiology and metabolism, and central neurochemical processes (51).

Detailed observations were acquired from research with the animal model. In 1940, Hetherington and Ranson were the first to recognize that the hypothalamus is involved in the central nervous regulation of food intake and body weight, in rats (56). Electrical destruction of the ventromedial hypothalamic area (VMH) led to increased food intake and a concomitant rise in body weight. Anand and Brobeck reported in 1951 that electrical destruction of the lateral hypothalamic area (LHA)
caused temporary aphagia and loss of body weight (57). It was hypothesized that the VMH- and LHA-lesioned animals shifted their set point of body weight from a higher to a lower level. Analogous to the case of involuntary dietary manipulations, the approach and the defense of the new body weight is achieved by adjustment in food intake (58).

The opposite effects of ablation of these areas are observed during electrical stimulation of the VMH and LH. Stimulation of the VMH leads to a decrease in food intake even in hungry animals whereas stimulation of the LHA elicits food intake even in satiated animals (59). These fundamental observations of VMH and LHA lesions on food intake and body weight led to the dual-center theory for the regulation of body weight and food intake by Stellar (60). In this theory, the VMH was considered to be a “satiety” area and the LH a “hunger” area. Basically, this theory holds true till the present time. However, many more brain areas appear to be involved and much more is known about the neural circuitry and the neurotransmitters and neuro-peptides involved in this circuitry. Also the role of the peripheral hormones informing the neural circuitry regarding the filling of the alimentary tract, the size of the reserves and the concentration of nutrients in blood circulation is more clear nowadays (61). Carefully reviewing the existing evidence of the LHA being a “hunger” area shifted this idea slightly towards the hypothesis that the LHA is also involved in motivation and reward. Besides regulating appetite and satiety, the hypothalamic areas (e.g., VMH, LH, para-ventricular area, dorso-medial hypothalamus, and arcuate nucleus) are involved in the control of release of neuroendocrine factors regulating the storage of absorbed nutrients, and release of the energy substrate glucose and FFA from liver and fat tissue (61). In this respect, the autonomic nervous system and the release of a variety of hormones, such as leptin (62), from the pituitary have to be considered as the main effector systems (61). In humans, pathologic effects like in craniopharyngioma patients, who show hyperphagia, has been related to dysfunctioning of leptin receptors in the hypothalamus (63), also indicating the hypothalamic function.

In humans, central and peripheral processes that affect hunger and satiety are signals during and after ingestion of food; respectively leading to sensory specific satiety, sensory satiety, and postprandial and post-absorptive satiety. Moreover, hunger and satiety are affected by external factors that also affect energy expenditure, such as physical activity, hypobaric hypoxia, and increased environmental temperature.

**Sensory Specific Satiety**

After feeding to satiety, humans reported that the taste of the food on which they had been satiated tasted almost as intense as when they were hungry, although much less pleasant (64). Analyzing the neural control of feeding in the macaque monkey (*Macaca fascicularis*) by recording the activity of single neurons during feeding has shown that a population of neurons in the lateral hypothalamus respond to the sight and/or taste of food only when the monkey is hungry (64,65). The modulation of
reward of a motivationally relevant sensory stimulus such as the taste of food by motivational state, for example hunger, appears to be an important way in which motivational behavior is controlled (64–66). The subjective correlate of this modulation is that food tastes pleasant when hungry, and tastes hedonically neutral when it has been eaten to satiety (65). Activity in the primary taste area (frontal opercular and insular taste cortices as well as the nucleus of the solitary tract) does not reflect the pleasantness of the taste of a food, but rather its sensory qualities independently of motivational state (64,66,67). On the other hand, activity in the secondary taste area (the caudolateral orbitofrontal cortex) and in the lateral hypothalamus are modulated by satiety, and may be related to whether a food tastes pleasant, and to whether the food should be eaten (64,66,67).

With respect to the representation of flavor, convergence of olfactory and taste inputs has been shown (68). There are regions in the orbitofrontal cortex of primates where the sensory modalities of taste, vision, and olfaction converge, and in many cases the neurons have corresponding sensitivities across modalities (68). In these areas flavor representations are built, where flavor means a representation, which is evoked best by a combination of gustatory and olfactory input (63,68).

It was also found in humans that the pleasantness of the taste of food eaten to satiety decreased more than for foods that had not been eaten. This implicates that if a variety of foods is available, the total amount consumed will be more than when only one food is offered repeatedly (69). This effect has been termed "sensory-specific satiety" (69). This effect is distinct from alliesthesia, in that alliesthesia is a change in the pleasantness of sensory inputs produced by internal signals (70), whereas sensory-specific satiety accounts for, at least partly, the external sensory stimulation received and is, at least partly, specific to that stimulation (64). Sensory-specific satiety occurs for the sight as well as for the taste and odor of food (64).

The enhanced eating when a variety of foods is available, may have been advantageous in evolution in ensuring that different foods with important different nutrients were consumed. However, today in humans, when a wide variety of foods is readily available, this can lead to overeating and obesity.

**Sensory Satiety**

In addition to sensory specific satiety, a relationship between sensory perception and food preference, respectively satiety has been shown in rats (71).

Perception of polyunsaturated fatty acids (PUFAs) has been demonstrated showing that these PUFAs inhibit delayed rectifying K\(^+\) channels (DRK channels) in mammalian taste receptor cells (71). Interestingly, the effects were only seen for cis-PUFAs (arachidonic, linoleic and linolenic acid). Moreover, DRK channels in tongue tissue of rats with a preference for high fat diets (Osborne-Mendel rats) were less sensitive to the cis-PUFAs, than DRK channels of rats preferring diets high in carbohydrate (55B) (72).

In humans, fat-specific satiety during dinner with oil containing linoleic acid vs. oil containing oleic acid was shown after a 2-week treatment with one of the oils.
but no change in general satiety (73). Moreover, we showed differences in taste perception in humans using a low concentration of linoleic acid. Tasters appeared to terminate eating a food, containing linoleic acid by satiety, whereas non-tasters terminated eating by a decrease in pleasantness of taste (74).

**Satiety in the Postprandial Phase**

With respect to the postprandial phase of satiety, the integrated role of gastric distension, emptying, and contractions within the complex series of physiologic and biochemical events surrounding meal patterning recently is being recognized (50,75,76). A role of the stomach in hunger and satiety was shown in that increases in hunger ratings are associated with the time that 90% of the test meal had emptied from the stomach (50). Foods emptying slowly from the stomach have been suggested to sustain satiety and delay the onset of hunger in humans (76). Gastric emptying may play a role in this relationship, although it is likely that gastric sensations interact with related factors such as the subsequent delayed (and thus prolonged) elevation in blood glucose (50,77,78). It has been suggested that gastric stretch receptors and contractions indicate the volume of stomach contents to the organism, whereas various peptides secreted from, or induced by, the alimentary tract indicate energy content. Such peptides include food intake inhibitors such as cholecystokinin (CCK), serotonin (5-HT), corticotrophin-releasing factor (CRF), somatostatin, enterostatin, bombesin, glucagon, and glucagon-like peptide (GLP-1 and -2). GLP-1 for instance, is related to the control of insulin, and to satiety, but its effect is diminished in the visceral obese (50). For some of these, it has been questioned whether the experimental results of hypophagia were actually caused by satiety, or by nausea induced by non-physiologic quantities of the peptides (50). Other peptides believed to stimulate food intake include neuropeptide Y (NPY), galanin, and endogenous opioids. It may be that, in general, peptides, which reduce food intake signal via the central nervous system to the ventromedial hypothalamus (VMH), and peptides, which stimulate food consumption may signal through the central nervous system to the lateral hypothalamus (LH) (50).

The presence of food, particularly fat in the upper small intestine stimulates the release of CCK, which has both peripheral and central receptors (79,80). CCK is known to serve regulatory roles in bile secretion, gastric emptying, and the exocrine pancreas. Additionally, CCK relays signals to the brain through the vagus nerve, inhibiting eating behavior in humans, causing meal termination (81). Conversely, as nutrient delivery to the intestine decreases, CCK release and vagal activity are reduced, so that eating behavior is no longer inhibited. Antagonists to CCK have been shown to increase food intake in rats, whereas CCK stimulants have been shown to decrease food intake in both rats and humans (50).

In rats, increased serotonergic (5-HT) transmission has been shown to decrease food intake, acting peripherally, and possibly via the central nervous system (CNS) as well. In humans, the hypophagic actions of serotonin have been studied extensively. Synthesis of 5-HT in the brain depends on the availability of tryptophan, its amino
acid precursor. Thus, dietary factors influencing blood tryptophan concentration may influence 5-HT synthesis. Such dietary factors include other amino acids, which compete with 5-HT uptake across the blood-brain barrier, and carbohydrate, which may have a diluting effect on tryptophan concentrations. Some data indicate that the hypophagic actions of serotonin work pre-absorptively, possibly through interactions with CCK and enterostatin (50). Dexfenfluramine, a pharmacologic anorectic agent previously used in weight-loss treatment in humans, acts by increasing the release of serotonin from presynaptic terminals, and blocking its re-uptake. Changes in serotonin metabolism have been reported in many cases of individuals with disordered eating, including anorexia, bulimia, obesity, and type 2 diabetes mellitus. Some investigators have proposed that serotonin may play a role in macronutrient preferences, including carbohydrate cravings, and fat avoidance, but this has been refuted by others (50). CRF (corticotrophin-releasing factor), a 41-residue peptide located in neurons throughout the brain, particularly the paraventricular nucleus, is believed to suppress food intake, and also to stimulate thermogenesis (82–84). These actions may occur via the sympathetic nervous system and/or via mediation of the actions of serotonin. Interestingly, alterations in the responses of adrenocorticotrophic hormone (ACTH) and cortisol to CRH have also been reported in some conditions of disturbed eating behavior such as anorexia nervosa (86). It has also been suggested that CRF, which is stimulated by exercise may mediate the effects of post-exercise anorexia, and elevated energy expenditure, being strongest immediately following a bout of exercise (82–84). Another situation of CRF release is during the stress response; therefore, CRF may be a factor in the down-regulation of food intake during stress, possibly along with noradrenaline (82–84). The most potent endogenous appetite stimulant known in humans thus far is NPY, which acts through the central nervous system, possibly through noradrenergic mechanisms (50). High levels of NPY have been found in the human hypothalamus (87). In both rats and humans, starvation is associated with elevated levels of NPY, which are reversed by refeeding. Some investigators have suggested that disturbed patterns or activity of NPY may occur in patients with anorexia and bulimia nervosa (50).

Galanin, another peptide with hyperphagic actions, is secreted from the intestine and islets of Langerhans, relaying signals to receptors in the paraventricular nucleus (88). In both animals and humans, it is recognized that some kinds of stress can reduce food intake (possibly mediated through CRF) whereas other types of stress can stimulate food intake (88). Endogenous opioids (beta-endorphin, dynorphin, and encephalins) are believed to induce stress-related hyperphagia, acting on several sites in the hypothalamus. Some data, but not all suggest that these compounds may influence meal size and macronutrient preference (for fat rather than simple carbohydrate) in humans (89).

Satiety in the Postabsorptive Phase

Once nutrients cross from the intestinal tract into the blood and become available for metabolism, they may exert postabsorptive food intake regulatory signals. Satiety
and hunger seem to be related to metabolic events surrounding nutrient processing, utilization, and storage (50). Thus, it logically follows that carbohydrate, with its rapid uptake and metabolism, would play important roles in short-term food intake regulation. For example, carbohydrate stores in humans range from approximately 150 to 500 g, depending on body size, exercise, and state of nutriture (50). This is rather low in relation to the 200 to 500 g of carbohydrate consumed in a typical daily diet. Conversely, the amount of fat and protein in the body are quite high in relation to daily dietary intake. Given each of these relative turnovers, and the complete dependence of the CNS on glucose as a metabolic fuel, the role of carbohydrate, particularly blood glucose, i.e., the regulation of food intake and energy balance has long been an intense focus of research (50). In the 1950s, Jean Mayer conducted an elaborate series of experiments in mice and rats, which led to the formulation of the glucostatic theory (90-92). Based on blood glucose concentration or arteriovenous differences, he postulated that the rate of glucose utilization by privileged brain regions determined nutrient ingestion (90-92).

When blood glucose was monitored continuously in fasting, time-blinded humans in 89% of the cases, transient declines were associated with spontaneous meal requests or changes in hunger ratings (50). This technique has been extended for longer durations, in the postabsorptive and postprandial states, throughout inter-meal intervals, and during exercise in time-blinded humans. As would be expected, the shape of the glucose curve varied following ingestion of different macronutrients, e.g., a 1,000-kJ drink of simple carbohydrate produced a sharp rise and subsequent fall in blood glucose. These characteristic rapid drops in blood glucose following the postabsorptive rise have been termed “dynamic declines” because they do not originate from a stable baseline, as do transient declines. During these dynamic declines in blood glucose, meal requests occurred in 87% of the cases (78). When an isovolumetric, 1,000-kJ, high-fat drink was consumed, the increase in blood glucose was more gradual and prolonged. The next spontaneous meal request came during the dynamic decline, which followed the drink-induced rise. However, because the rise and fall in blood glucose concentration was longer following the high-fat drink than the simple carbohydrate drink, the second meal request came later following the fat drink. Despite the different meal intervals in relation to this macronutrient composition, ad libitum energy and macronutrient intakes did not differ. These interactions have been proposed as early as 1916, by the originator of the glucostatic theory (93). More recently, the term “glucodynamic” has been proposed as a more accurate reflection of the responses of the brain (and perhaps liver) to continuously changing blood glucose, and metabolism in general, and of the processes by which different systems within the organism are integrated in metabolic regulation (76). Evidence thus far indicates that patterns of plasma glucose, particularly the transient and dynamic declines, play a role in determining meal initiation and intermeal interval. Thus, views of glucose’s role in food intake regulation have shifted from that of a satiety signal to that of a meal initiation signal (50).

Maintenance of adequate carbohydrate within the body is of vital importance (particularly to the CNS), yet the amount of dietary carbohydrate consumed each
day is similar to the amount stored as glycogen. Therefore, a “glycogenostatic” theory of food intake regulation has emerged, based on the notion that the body adjusts its food intake such that ample glycogen stores are maintained (50). The original data supporting this theory came from studies in mice, but have not been confirmed in all studies in humans. Recent data have suggested that when glycogen stores are depleted by exercise, or by energy intake restriction, the relationship between blood glucose patterns and meal requests is disturbed perhaps due to removal of the carbohydrate buffer reserve (50). It may be that the goal of maintaining ample blood glucose for normal CNS functioning as predicted by the glucostatic model by Mayer could be considered as an additional daily goal. Because the glucostatic and glycogenostatic models complement each other, this may be example by which long-term food intake regulation is a summation of short-term regulations.

ROLE OF THE LIVER IN METABOLIC CONTROL OF FOOD INTAKE

Although hepatic metabolic signals are not necessary to maintain food intake and body weight, a large body of evidence indicates that such signals play a role in the control of eating (94). Total parenteral nutrition and peripheral administration of various metabolites (e.g., glucose, pyruvate, lactate, hydroxybutyrate) generally inhibit eating. On the other hand, metabolic inhibitors such as the glucose antimetabolite 2-deoxy-D-glucose, fatty acid oxidation inhibitors (etomoxir), the fructose analogue 2,5-anhydro-D-mannitol (2,5AM), and the sodium pump inhibitor ouabain, have been shown to stimulate eating under various conditions (94). Many of these effects are particularly pronounced when the substances are infused into the hepatic portal vein, and are markedly attenuated when the hepatic branch of the vagus is disconnected (94). This suggests that the observed effects on eating originate in the liver and are mediated by hepatic afferent nerves. In addressing these issues, it must be kept in mind that the hepatic afferent nerves involved are also part of a complex network that plays an important role in blood glucose regulation, electrolyte/fluid balance, and other regulatory systems, which may interact with mechanisms of food intake control (94).

SUGGESTIONS FOR FUTURE RESEARCH

Obesity

• Given the lack of success with respect to body weight management on a group level, future research might deal with subject-specific prevention and treatment of obesity, including weight maintenance thereafter.
• Subjects might be characterized with respect to behavioral and genetic predisposition of obesity.
• Subject-specific metabolic effects related to body (core) temperature or core-skin temperature gradient in response to changes in, e.g., ambient temperature, or thermogenic ingredients might be assessed (95).
When aiming for energy intake reduction, reduced energy intake might be set and sustained satiety might be aimed for, instead of expecting spontaneous energy intake reduction after increasing satiety.

For weight maintenance an increase in cognitively restrained eating might be supported by stimulating a decrease in general hunger (96).

Food Intake

Future research with respect to food intake might include the relationship between taste and texture perception, appreciation, and satiety.

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DISCUSSION

Dr. B. S. Ramakrishna: You mentioned that there were satiety signals from the liver. Could you just elaborate on some of them?

Dr. M. Westerterp-Plantenga: Well, in the first place I have to mention that satiety signals from the metabolism have been shown mainly by Wolfgang Langhans in the very late phase of the inter-meal interval. You get some late satiety signals, especially when the fat is oxidized, in the liver, and that gives a new signal to be able to extend the inter-meal interval.

Dr. B. S. Ramakrishna: Would this happen to be like a liver disease, do you know? Because normally, people come to us, practising in gastroenteritis, and say, I have reduced appetite, I think there's something wrong with my liver. Would you think there is something to that?

Dr. M. Westerterp-Plantenga: Yes, since it has been found that the metabolic satiety in response to feeding in patients with liver transplantation has changed. This may be a consequence of hepatic denervation.

Dr. Y. K. Amdekar: There are children or patients who come to feel they're not having a normal appetite and they blame it on their liver dysfunction.

Dr. M. Westerterp-Plantenga: Well, I think that yes, they might be right, but there has been some work done on making people conscious of their appetite feelings, and this involved giving them a visual analogue scale, in which they rate hunger and satiety during the day and they learn how to detect feelings about hunger and about satiety, so that they might see their own pattern during the day. When they learn about their own pattern, they know when they can have a meal or when they should not have a meal. However, there is some evidence that when liver functions are disturbed, satiety signals are lacking at some place.

Dr. Luciano Tato: Energy consuming is most important, but maybe sometimes with athletic condition size is important for performance too. Rhythmic athletes need a different body profile from swimmers and this is obtained by fasting, not by energy consuming only.

Dr. M. Westerterp-Plantenga: Did I understand the question, that at least energy intake is not caused by hunger or satiety, but it has been learned in order to increase performance?

Dr. Luciano Tato: Yes, but sometimes the training is obtained with fasting too, not only with energy consuming.

Dr. M. Westerterp-Plantenga: In athletes, it's surprising how very high the energy expenditure can be. When you measure energy expenditure during hard performance periods like the Tour de France or the Whitbread Sailing Race, it would come on an average of four to five times the resting metabolic rate, so that provides the cause of a very high energy intake, and the only way to reach this very high energy intake is to consume high energy-dense foods. It's not that the athletes are so hungry, because normally they lack hunger, especially in this post-exercise anorexic period, but they know they have to eat, otherwise they won't be able to perform.

Dr. George Fuchs: Dr. George Fuchs: I know you mentioned it, but I didn't hear about it in terms of the macronutrient composition of diets and their effect on satiety. Certainly in the United States, there are many weight reduction programs that emphasize high protein intake and the generation of a kytoic state, and so there's this emphasis on protein intake at the expense of some of these others for pro-weight reduction. What are your views on that?

Dr. M. Westerterp-Plantenga: Yes, you're right, high protein is very satiating. In fact, one slide that I skipped showed the satiating power of protein, and in addition to that, there is a sort of an energy efficiency related to protein. Energy efficiency is the highest with normal protein intake, which is about 15 energy percentage of the day. With a lower protein intake,
and a much higher protein intake. Energy efficiency is lower. This means that you can eat more of a very low or high protein diet before you put on a lot of weight. This follows the stock hypothesis that was described a couple of years ago, in the International Journal of Obesity.

Dr. Wolf Endres: These data on the fatty acid tastes. This is very interesting. Are you aware of studies in infants receiving formula with and without linoleic acid?

Dr. M. Westerterp-Plantenga: No, these are the very first studies that have been executed and at the moment we have tested about 200 subjects, and we are about to do tests in children as well, but that's the only thing that has been done. The main trials on this topic so far have been with rats.

Dr. Shrichandra Bhawnani: I have two questions. One is that in our part of the country, worm infestation is a very important cause of hydration and satiety. Parents complain that children have lost weight or they have hydration satiety or hunger because of Giardia and also fascioliasis, and when we have given anti-diarrhea treatment, we have found that there is a return to normal. Does this have anything to do with this pattern? And number two, is there any study on the use of non-absorbable fat in the treatment of obesity?

Dr. M. Westerterp-Plantenga: Back to your first question. It is very difficult when you are underweight to keep up your energy intake, but when you increase physical activity a little bit in these children, then it's much easier to increase energy intake, if that's possible, but I'm not very familiar with the type of disease you are talking about. And your second question was about non-absorbable fat. I think it was mainly in the 1980s that many of the experiments on non-absorbable fat were executed and the non-absorbable fat was designed to have more or less the same properties as fat, in that it melted in the mouth and it gave the same texture to the food that you were eating. There have been as many studies showing compensation for ingesting non-absorbable fat as showing non-compensation, so there were divided opinions on whether to apply it or not. In the United States, it has been applied. In the Netherlands it was not allowed to be used in foods. From recent research we get some indications that when you use these non-absorbable fats, you also lack later satiety signals, so in the end, the satiety feeling might be less and that might be a reason for compensatory behavior after that.

Dr. Shrichandra Bhawnani: Would you be more clear on this: that whether the effect of fat on the hydration on the satiety is due to a local effect, or because of the level of the blood hydration? May I have clarification again on what effect fat has on satiety. Is it because of the local effect or is it because of the hydration of the serum lipid level?

Dr. M. J. Farthing: What is the mechanism by which fats reduce satiety locally in the gut?

Dr. Shrichandra Bhawnani: If it is because of the local effect, we can do very well with the non-absorbable fat, but if it's because of the hydration in the serum level, then the non-absorbable fat would not be the main step in the treatment of obesity and can't even be thought of in the treatment of obesity.

Dr. M. Westerterp-Plantenga: The contribution of fats to satiety is, as we have seen yesterday, by affecting CCK and also by its metabolic effect in the liver, and it mainly determines the inter-meal interval, but it does not determine meal size at that very moment.

Dr. J. G. Farthing: Does non-absorbable fat trigger CCK? Does olestra trigger CCK?

Dr. M. Westerterp-Plantenga: No.

Dr. George A. Bray: A very lovely discussion of both the intake and expenditure side and you point out one of the dilemmas of going from the single-meal effects to the longer term energy-balanced ones with our current techniques. I wanted you to address the way in which we're going to solve that problem, because it's obviously the one we need to deal with, if we're going to understand this epidemic. That is, what do we need to do to get an understanding
of what breaks down over time as opposed to the single-meal incident. And we might get some insight into that from the difference in rates of weight-gain in your country and in fact all of the ones north west of you, Denmark, Sweden, Norway appear to have a very much lower or almost no increase in obesity over the last 15 years, while the countries south of you, Germany, France, England, Italy, Spain all show this epidemic, as does the US, and does that give us some insights? So can you tell us how we’re going to approach it scientifically and epidemiologically and does your experience in your country help us understand this epidemic and what we do about it.

Dr. M. Westerterp-Plantenga: Different rates of weight gain have been shown. The lowest, but still significant rate of weight gain is 0.3 kg/yr, and then the rate of weight gain, which is really disturbing, is almost 1 kg/yr, and you can always discriminate between people who have gained 10 kg over the last 10 years and people who have hardly gained any. One thing that we think is that there is a genetic component behind this, but such a genetic component might only contribute for 35% or 40%. Another thing is the physical activity, as I mentioned already. In physical activity, there is a geographical and the seasonal component and it works both ways. If it gets colder, one needs to work harder to achieve something or to go somewhere. If it gets warmer, you also have the opportunity in another country to do some more things outside. So the cold season as well as the warm season can both stimulate physical activity, whereas in the southern countries it’s the warm season that does not stimulate physical activity. In our studies about ambient temperature, we have found that when you increase ambient temperature, there is an effect on core temperature and people tend to compensate this effect on core temperature. In fact, when you increase ambient temperature, core temperature tends to go up and people try to prevent this increase by under-eating and by being very inactive. If there is both under-eating and being inactive, when the inactivity then prevails, there might be a trigger for causing obesity, although under-eating is still a factor. Also, in the cold environment, when people start over-eating to prevent decrease of core temperature, this might cause an obese effect. So I do not have a very clear answer, but the main difference is physical activity.

Dr. Peter Nienan: I agree with you that physical activity is important, but the biggest obstacle we’re having in Canada at least, is to make it happen in terms of schools and cutbacks with physical education classes. I’m interested to learn from your experiences in Europe, can you share with us some of your successes with getting children to become more physically active?

Dr. M. Westerterp-Plantenga: Now your environment plays a role of course. When children can be outside the school and play in the street, then the environment has to be safe and either the environment is safe already, considering traffic and other possibilities, or one has to collaborate with the government and claim an environmental situation that provides the possibility for an increase in physical activity, and I think the latter is very important. For instance, in Australia there is some action now, and Boyd Swinburn is one person behind that, who tries to give suggestions to the government for a physically active, friendly environment, and that’s really important.

Dr. Mirdula Chatterjee: I have a couple of questions for you. Number one, it has been shown in various studies that the part of metabolic handicap may relate to selective deposition of abdominal fat. What is the explanation for this?

The second question is, there is a clear consistent relationship between low socio-economic status in early life and increased fatness in adulthood in developed countries. It is just the opposite in developing countries. Will you please explain, why?
The third question; is there any study done in Indian children regarding obesity, its incidence or its causes?

Dr. M. Westerterp-Plantenga: Yes indeed, several studies have confirmed this. A probable explanation is its specific localization (portal fat) combined with a higher turnover rate of visceral fat compared to subcutaneous fat. However, whether there is a causal relationship is still a matter of debate. The last question you asked, whether there is any evidence for development of obesity in children in India. I'm not aware of any epidemiological studies on that. There might be some, but I do not know about them.

Dr. Mirdula Chatterjee: What I want to know is if the International Obesity Task Force (IOTF) has done any study among Indian Children?

Dr. Y. K. Amdekar: She wants to know about the Indian children settled in the US, whether there is any study in that ethnic group.

Dr. M. Westerterp-Plantenga: I'm not aware of a study like that. No, I'm sorry.

Dr. Mirdula Chatterjee: My first question was, the part of the metabolic handicap relates to selective deposition of abdominal fat. Any explanation?

Dr. M. Westerterp-Plantenga: Yes, I haven't explained much about body fat distribution, but abdominal fat, the visceral fat is far more complicated with metabolic sectors than the subcutaneous fat on the hips. Fat distribution expressed as weight-hip ratio is also very important and in a low waist-hip ratio, a higher percentage of fat is still far less dangerous than a higher waist-hip ratio.

Dr. Marcello Giovannini: I ask you about the prevention of obesity, because we observed that breastfeeding has a negative correlation with obesity. How long can breastfeeding be maintained without causing higher obesity? The other question is, we have observed (a) that protein intake in 1 year olds and the development of obesity in the high-risk family, that there was a correlation of 4 years and 8 years with the protein intake at the 1-year-old stage and also by gender, with the father's fatness being more significant than the mother's, because the father has more influence on the development of obesity. Do you agree? I would like to hear your opinion please.

Dr. M. Westerterp-Plantenga: You were referring to the relationship between the fatness of the father or the mother. Yes, there are some studies that have assessed that, but they did not find a correlation with the fatness in the children, when only one of the parents was obese. They only found this correlation based in the children, when both parents were obese, but of course you may be right, but I'm not aware of the studies.

Dr. Christoph Beglinger: Coming back to the linoleic acid story, can you tell us the percentage of people who can taste versus the ones who cannot taste?

Dr. M. Westerterp-Plantenga: Yes, this is preliminary, because we are still doing the calculations on that. Among the first 60 people, we found a constant percentage of 60% tasters and 40% non-tasters, but now since we have covered far more people, we find about 50% tasters and 50% non-tasters, but I still admit immediately that it is related to age. In the younger people you find 70-80% tasters. In the older people you find 30% tasters, so it seems that it's something that disappears with age, and it also appears to be related to body mass index, which is a peculiar relationship. Within a normal to slightly over weight body mass index, the tasters have a lower body mass index, so between a body mass index of 20 to 29, the tasters have the lowest body mass index and the non-tasters have the highest body mass index. But then when you look at a body mass index over 29 it's different, then there is no clear relationship. So it seems that once you have a high body mass index, this possible mechanism disappears or is ignored.

Dr. George A. Bray: Let me comment after your role in dietary fat and obesity. You now
are the adviser to the minister of health in the Netherlands, or any other country and he asks you, what level of dietary fat should we recommend to the public. What’s your advice to him and why?

*Dr. M. Westerterp-Plantenga:* My advice would be that it is 30%, because when people tend to enlarge it a little bit and they tend to go to 32% and 33%. I do not think that only the lower percentage of fat might be responsible for body weight maintenance. It also implies a higher percentage of carbohydrate and protein, and the latter might prevent body weight increase.

**REFERENCE**