REVIEW ARTICLE

The global obesity epidemic: Snacking and obesity may start with free meals during infant feeding

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Abstract

Feeding is vital for survival. The brain has strong hunger and reward mechanisms that ensure optimal food intake for adequate nutrition. The drive for feeding is particularly strong in humans whose large brains require large energy support. This starts immediately after birth; the newborn child being able to taste sucrose and suck the sweet and fat from its mother’s milk. At present, mothers are generally advised to breastfeed children as often as they like, which may be up to 15 times a day. At the same time, childhood obesity is rapidly developing. One reason for the rapidly increasing prevalence of childhood obesity may be overfeeding with snack food.

Conclusion: We hypothesize that non-rule breastfeeding favours the development of snacking throughout the day during childhood, a habit which in turn favours the development of obesity.

Key Words: Appetite regulation, hunger, obesity, reward, satiety, snacking, sucrose

Introduction

The global epidemic of overweight (BMI >25) and obesity (BMI >30) is a worldwide concern. All its consequences, such as shortened life expectancy due to insulin resistant diabetes and cardiovascular disease, are now well known. In addition, subjects with obesity suffer from reduced physical capacity, destruction of the hips and osteoporosis. At present, it is calculated that half of the Swedish male and one-third of the female adult population is overweight. Obesity is also a chronic disease.

Worldwide concern about the rapidly increasing prevalence of overweight and particularly of obesity is mirrored by the enormous amount of articles regarding this subject in the medical literature as well as in magazines and daily newspapers. Politicians make numerous statements about the importance of controlling obesity, and the medical profession has been holding repeated seminars and congresses on the subject. For instance, in June 2005, the 14th annual European Congress on Obesity was held in Athens, Greece, attended by around 1000 delegates. Last year, the 13th congress was held in Prague, Czech Republic, with about the same number of delegates. At these congresses, epidemiological, endocrinological and behavioural aspects including various therapeutic approaches such as surgical intervention and the use of proton leakage drugs are reported in numerous oral presentations and poster sessions. Due to concern about the consequences of obesity, the effort to study the prevalence of obesity and its control is rising at an exponential rate. It is easy to tell people that they should eat less and not more than they need, but it
seems impossible to change current human eating behaviour.

There is substantial evidence that overweight and obesity have their origin in childhood. In fact, attention to childhood obesity was first given by Hilde Bruch in the USA, who, at the end of the 1930s, reported that childhood obesity is often associated with psychiatric disorders and signs of social maladjustment in the family \cite{1,2}. She was of the opinion that psychiatric health hazards may occasionally constitute a primary factor in the production of obesity. She also pointed out that obese children are subjected to conflicts and tension in their relations to the rest of the family, and that they lack sufficient understanding of their corporeal handicap. She concluded that obesity constitutes such a serious physical health problem that a restricted and regulated regimen, such as dietary intervention, is indicated. Treatment should primarily concern the obese child and not merely its obesity. However, as found by Mossberg in 1989 in a 40-y follow-up of overweight children, it is evident that a high percentage of the subjects who were overweight or obese during adolescence remained overweight as adults \cite{3}. He also noticed that the obese adolescents who remained obese as adults had a food intake in accordance with recommended levels \cite{3}. As obesity during adolescence is associated with higher-than-expected morbidity and mortality levels in adult life, he concluded that weight-reducing methods should be started early in life \cite{3}.

In addition to rapidly increasing consciousness about the high prevalence of obesity in adults and children, the results of follow-up studies like Mossberg's have led to current concern for the consequences of childhood obesity. As it is widely accepted that, in most instances, overweight starts in childhood, many attempts have been made to identify relevant risk factors during childhood. For instance, in this issue of *Acta Paediatrica* it is reported that the ratio of childhood obesity increases with television viewing, parental obesity and high birthweight, and that it decreases with longer duration of sleep, high maternal and parental education, and a higher number of siblings \cite{4}. Thus, education about energy demand and energy expenditure should in particular be given to families with high-risk children, i.e. to those having high BMI and high birthweight. As children in immigrant families are known to have a high risk of developing obesity, they should also be carefully followed up.

In another study, which is published in this issue of *Acta Paediatrica*, Eriksson et al. report that not only the incidence and prevalence of childhood obesity is gradually increasing but also the degree of obesity \cite{5}.

A large number of books on childhood obesity have been published in recent years \cite{6,7}. A considerable number of articles on the same subject have also been published in *Acta Paediatrica* in the last year \cite{8–19} and in the form of a supplement \cite{20}. In this connection, it should also be mentioned that the former Norwegian Prime Minister and Director of the WHO, Gro Harlem Brundtland, then a school physician, together with colleagues published a paper in *Acta Paediatrica* in 1975, where it was reported that the weight and height of Norwegian 10–11-y-old children had increased from 1956 to 1970 \cite{21}. This may be one the first observations of the increasing weight of school-aged children.

### Basis of appetite regulation

The strong drive for food, and particularly for rewarding types of food, depends on the basic energy requirements of the various organs of the body, of which the brain has the highest energy requirement per weight of tissue (Table I) \cite{22}. The energy consumption of the brain is overwhelming compared to adipose tissue and skeletal muscle. On a relative scale, the total energy consumption of the brain is calculated to be 40% in newborn infants, 25% in children and 10% in adults. It has also been suggested that the reason for large animal brains is the necessary high energy consumption. In fact, the size of the brain in primates is determined by the type of nutrients consumed. Primates eating fruit have larger brains than those eating leaves, which in turn have larger brains than those eating insects. Since fruit clearly contains energy, recognizable in the sweet taste, the inherent drive for sweet-tasting food has been necessary in the evolution of the human brain. We probably also have an inherent drive for fat, although fat may be secondary as an energy substrate.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Energy expenditure (kcal per day$\times$mass in kg)</th>
</tr>
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<tbody>
<tr>
<td>Brain</td>
<td>240</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>13</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>4.5</td>
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<tr>
<td>Bone</td>
<td>2.3</td>
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That our basic choice is directed towards carbohydrates and fat is evident from studies on the choice of macronutrients in countries with free access to different foods compared to that in countries where choice is restricted by external factors. Thus, in Nigeria, the consumption of carbohydrate is extremely high (83%), whereas that of protein and fat is low. In Greenland, on the other hand, carbohydrate consumption is extremely low due to the scarcity of carbohydrate. Instead, fat and protein are the main macronutrients consumed. Hence, protein...
has substituted the need for carbohydrate in Greenland. In the USA, as in other Western countries, the wide selection of available food leads to the choice of fat and carbohydrate in equal amounts, being around 45% each.

**Appetite-regulating signals**

**Hunger signals**

The *sine qua non* for survival is to consume food that can maintain energy balance and body temperature. This is achieved by a number of potent hunger signals, which are brought about by ghrelin, neuropeptide Y (NPY) and the orexins. They maintain the drive for food and are interrupted upon feeding (Figure 1).

Ghrelin is produced in L cells in the stomach and is thought to act as a meal initiator [23,24]. In humans, it has been shown that individuals who have lost 17% of their body weight via dieting have significantly increased ghrelin levels with an exaggerated response prior to meals [25]. On the other hand, obese patients who have been subjected to a gastric bypass operation and who have lost body weight have significantly reduced levels of ghrelin, and are more successful in keeping their reduced body weight [26]. Thus, rising ghrelin levels may serve as a critical signal to induce hunger during fasting. The site of action for ghrelin is thought to be in the hypothalamus, where ghrelin receptors are localized in the arcuate nucleus [27].

As the ghrelin level rises not only during fasting but also when a meal is expected or requested, the initiation of food intake is probably under neuronal control [28]. It has thus been found that ghrelin levels increase after sham feeding, i.e. when food is not entering the stomach. At the same time, gastric acid and pancreatic secretion is induced, which suggests that ghrelin is released through the activation of a central vagal nerve reflex [28]. Thus, hunger signals and hunger are stimulated by the expectation of food, by sucking and by chewing.

The most prominent property of ghrelin is the accumulation of fat mass with an increase in body weight [29]. An inverse relationship between obesity and plasma ghrelin levels has been demonstrated, for instance in obese Pima Indians who have reduced levels of plasma ghrelin, suggesting a defence mechanism against obesity [30]. High-fat diets are known to reduce the plasma ghrelin level, which in a similar way could be viewed as a mechanism to restrict food intake. In contrast, a low-protein diet or a fructose-containing diet has been found to increase the serum levels of ghrelin [24]. The hyperphagia induced by fructose in soft drinks may therefore be explained by an increased level of ghrelin to induce hunger. Thus, hunger signals are also released in a more specific way, being dependent on the type(s) of

Figure 1. Appetite regulation includes hunger and satiety signals. During fasting, various hunger signals are activated, such as ghrelin from the stomach and neuropeptide Y (NPY), the orexins and melanin-concentrating hormone (MCH) from the brain. At the same time, leptin and insulin levels rise and signal satiety through central mechanisms in the hypothalamus. The liver signals satiety through ATP production. Homeostasis occurs (middle picture). With palatable food, the brainstem not only gives signals to the hypothalamus but also to the reward centre, triggering a release of dopamine and opiate peptides. At the same time, the reward centre interacts with the hypothalamus to blunt the appetite-signalling system. Food intake is continued and non-homeostasis occurs (lower picture).
macronutrient in the food eaten. This fact is important since snacking often means consumption of sucrose and fat-containing products that are low in protein.

NPY is a neuropeptide secreted from the arcuate nucleus in response to fasting and when the demand for energy is increased, such as during lactation and exercise [31]. NPY is the first discovered hunger signal. The importance of NPY in mediating hunger is supported by the finding that hunger is reduced after prolonged fasting in NPY-knockout mice compared to wild-type animals [32]. Fasting increases NPY expression, but NPY expression is also raised by sucrose-containing diets [33]. On the other hand, fat, and particularly polyunsaturated fat, tends to decrease the expression of NPY [34]. Thus, hunger signalling is related to the type of macronutrient eaten; hunger being particularly promoted by sucrose.

Chronic infusion of NPY in animals produces obesity with hyperphagia and insulin resistance [35]. It has also been demonstrated that an increased NPY expression in the arcuate nucleus and the paraventricular nucleus (PVN) correlates with obesity and hyperphagia [36]. Both leptin and insulin inhibit the expression of NPY. Thus, leptin and insulin resistance may be important factors for explaining an increase in NPY expression leading to overeating during these conditions [37]. Since NPY is present only centrally, there is no study that links human obesity to increased expression of NPY.

The orexins are two peptides which are produced in the neurons of the lateral and posterior hypothalamus [38]. Intracerebroventricular injection of orexin increases food intake [38], but the central role of orexin in regulating feeding behaviour is less well defined. Expression of the orexins is increased by food restriction and fasting both in rodents and in non-human primates [39], suggesting a role in driving food intake following energy deficiency. A falling glucose level seems to be an important mediator for an increased orexin expression [40], hence linking falling blood glucose levels to hunger.

Melanin-concentrating hormone (MCH) is another hormone believed to be important in stimulating feeding and causing human obesity [41]. The target of MCH neurons are brainstem motor systems that are involved in chewing and swallowing. The neurons also act on parasympathetic ganglia that promote salivation as well as gastric and pancreatic secretion. MCH together with the orexins also promote awakening and arousal which increases the probability for animals to find and eat food [42].

To summarize, hunger signals are in general released during conditions of energy deficiency such as fasting and physical exercise. They stimulate food seeking and food intake, and disappear soon after the onset of feeding. Hunger signals are also released by the expectation of food, suckling and chewing. The type of macronutrient eaten, whether fat, carbohydrate or protein, influences hunger signalling.

### Satiety signals

Satiation is a slow process which starts in the gut and continues in other peripheral organs like the liver and adipose tissue. Several satiety signals have been identified, of which some will be discussed below. Humans eat in episodes, i.e. in meals or snacks, until they are satiated. In this state, the drive to eat is blocked transiently; the hunger drive is then gradually built up again. The start of the next meal is determined by several factors, not only by satiety signals, but also by environmental factors.

In understanding internal satiety, there are essentially two groups of satiety signals. Gastrointestinal peptides act as short-term regulators, whereas adipose tissue-relevant peptides such as leptin and insulin act as long-term regulators. The brain harbours the receptors and target mechanisms for the satiety signals (Figure 1).

One of the most important determinants of meal size is the weight or volume of the food eaten. Thus, stomach distension and fullness are important events during satiety. Most satiety-producing gut peptides act through an inhibition of gastric emptying, like cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1) and pancreatic polypeptide Y (PYY); cholecystokinin being the most likely mediator of this effect.

Cholecystokinin is released by the presence of fat or protein in the duodenum. The receptors of CCK are present on the vagal nerve, transmitting the signalling to the nucleus tractus solitarius and from there to the brain. CCK also suppresses appetite in humans in a dose-dependent way, as demonstrated in several studies [43,44]. The stomach must be filled in order for CCK to suppress appetite, pointing to the importance of the inhibition of stomach emptying for the effect of satiety. It has been suggested that CCK acts as a satiety agent for fat in humans, based on the observation that a blocker of the CCK receptor inhibits the satiating effect of intestinal fat [45]. Fat substitutes, however, do not release CCK [46], which may explain why satiety decreases.

Glucagon-like peptide 1 is another gut satiety peptide, which is produced in the caecum upon arrival of food products in the intestine. The activity of this peptide was first described as the “ileal break”, which implies that it inhibits intestinal motility from the ileum. This breaking is also involved in the satiating effect of GLP-1, as observed both in rodents and in humans. GLP-1 also exerts long-term appetite reduction when given subcutaneously for 6 wk [47]. The GLP-1 receptor increases its expression during high-fat feeding, suggesting a defence against overfeeding with a high-fat diet. Yet, there is no information...
on the role of GLP-1 in human obesity. In man, whey protein is more efficient than casein in the release of GLP-1 to produce satiety [48]. This function suggests that satiety is not only related to fullness of the stomach but also to the components of the food, whether fat, protein or carbohydrate.

PYY is a gut peptide released almost immediately after feeding, suggesting neural regulation [49]. It inhibits food intake both in rodents and in humans [50]. Obese subjects have reduced PYY levels compared to lean controls [51], suggesting that PYY is physiologically active as a meal terminator. There seems to be no specificity in the release of PYY, as it is released after carbohydrate-, fat- and protein-enriched meals. More studies are needed to understand the role of gut peptides in obesity.

Leptin and insulin—long-term regulators

The role of leptin in appetite regulation and energy balance is of central importance in view of the strong effects of disruption of the leptin gene or its receptor. Such defects have been identified both in animal and human obesity. Plasma leptin levels in humans correlate positively with total fat stores [52], which means that obese subjects have elevated levels of leptin compared to normal-weight subjects. This fact suggests some type of leptin resistance; a condition which has also been demonstrated in certain downstream intracellular events following the activation of the leptin receptor. Leptin function has actually been re-evaluated, being a feeding signal when its concentration is low, rather than a satiety signal when levels are high. Thus, focus has been on the ability of the appetite regulation system to trigger hunger when levels of leptin are low. A satiety function of leptin seems unimportant from an evolutionary point of view, as concluded from the markedly low levels of leptin in free-living primates [53]. Instead, by low leptin concentrations, the energy balance is meant to be restored during fasting [54]. In intervention studies, appetite has been found to be reduced after the administration of human recombinant leptin in semi-starved overweight men [55]. Thus, leptin is important for the regulation of appetite during energy restriction.

Insulin may also play a role in the long-term regulation of energy balance [56]. Thus, centrally injected insulin has been found to suppress appetite. The postprandial increase of insulin levels allows the hormone to pass the blood–brain barrier and to reach its receptor in the hypothalamus, whereby satiety is induced. The fact that obesity is associated with reduced passage of insulin through the blood–brain barrier explains the attenuated effect of insulin in suppressing appetite in obese subjects [57]. When insulin acts centrally, it reduces the eating of palatable food, i.e. food containing fat and/or sucrose [58,59]. Since insulin resistance is often associated with obesity, the overeating of palatable food may be a consequence of central insulin resistance.

Estimations of insulin levels in blood cannot, however, predict satiety, since levels of insulin reflect many different metabolic processes, including anabolic reactions [60].

In summary, gastrointestinal satiety peptides act by inducing satiety in response to large-volume meals. The small-size meals of “snacking” are therefore not enough to promote satiety. It should be kept in mind that gastrointestinal satiety signals act not only to inhibit gastric emptying but also centrally to release serotonin, causing satiety and sleepiness. Hence, small-size snacking does not produce satiety centrally, either. The role of the long-term regulators leptin and insulin in inducing satiety is more complex. Instead of promoting satiety, leptin seems to be the most important hormone for allowing hunger signalling during energy deficiency due to its low levels. Insulin promotes satiety when acting centrally and energy storage when acting peripherally. The action of insulin as a satiety signal therefore depends on whether it can pass the blood–brain barrier to reach central receptors. More studies are needed to clarify the complex role of leptin and insulin in appetite regulation.

Whereas appetite-regulating peptides are involved in energy balance by linking eating to the energy state of the body in a homeostatic process (Figure 1), another process tilts the energy balance of the body by the overconsumption of food, leading to weight gain. This overconsumption is mostly associated with specific food habits, such as the consumption of fast/junk food outside the home, in particular of fatty food in combination with sweet soft drinks. Homeostatic maintenance is replaced by non-homeostatic eating (Figure 1).

Eating, appetite signalling and reward system

Non-homeostatic eating

Food that is rich in fat and sucrose is attractive, and thus easily promotes overeating and obesity. Numerous studies have demonstrated that palatable food triggers appetite. Sweet taste, from sucrose or from artificial sweetener, stimulates appetite when given as a drink before a free-choice buffet [61]. Sucrose dissolved in fluid is a more potent trigger of appetite than in solid form [62]. In a similar way, high-fat diets lead to overeating, as demonstrated in rodents [63] and humans [64]. Reward eating is characterized by prolonged eating of numerous small bites instead of a single large meal, a condition termed passive consumption. Such non-homeostatic eating has two consequences: (1) it triggers the reward system in the
brain and (2) it weakens the regular appetite-signalling system.

Triggering of the reward system

The mechanism for the activation of the reward system by consumption of palatable food is coupled to the stimulation of various “classical” reward neurotransmitters, such as dopamine in the nucleus accumbens or the opiate system which has connections to several brain systems (Figure 1). The reward of eating food has been compared to that which is induced by drugs. In both conditions, increased consumption leads to craving, followed by symptoms of abstinence and anxiety during withdrawal. It has also been suggested that the consumption of sweet and palatable food is motivated by its capacity to relieve stress. High-fat food increases the expression of various opiate peptides such as prodynorphin and dynorphin in the arcuate nucleus, known to relieve stress [65]. The injection of opioids, which are both μ-receptor and κ-receptor agonists, stimulates the intake of high-fat instead of low-fat food [66]; a finding that supports the hypothesis of a positive circuit of feeding and the importance of reward in fat consumption. The injection of opiates in rats can also induce the choice of sweet-tasting food, which supports the view of a vicious circle in which opiates stimulate the intake of sucrose.

The view that opioids are released in response to the ingestion of palatable food, in particular of sweet food, is supported by the discovery that naloxone, an opioid antagonist, is highly effective in reducing food intake in individuals who binge on sweet high-fat foods such as chocolate and biscuits. The involvement of the opioid system suggests a strong motivational force to select and eat palatable food, as has been demonstrated in bar-pressing experiments in which an increased breaking point has been observed when palatable food is ingested. In contrast to the situation with sucrose, no evidence of addiction to or dependence on fat has been reported. Thus, signalling following fat intake may differ from the sucrose reward reaction by being self-regulating or self-limiting.

In summary, the intake of palatable food stimulates the internal reward system of the brain leading to overconsumption. It seems that sucrose, particularly in the form of sweet drinks, is more potent than fat in triggering the reward system.

A weakening of regular appetite signalling

A second reason that palatable food stimulates the appetite is a weakening of regular appetite signalling [62]. The number of reported instances of a faulty or blocked response to palatable food is increasing. Thus, sucrose consumption has been found to stimulate ghrelin expression, which suggests that sucrose consumption increases hunger instead of satiety [62]. There is an accelerated gastric emptying following sucrose feeding, which means that the gut regulatory system is weakened and a larger meal needed to reach satiety. In addition, there is an important long-term adaptation to palatable food, which means that appetite signals related to meal taking are blunted [62]. Thus, elevated ghrelin levels following fasting are not suppressed after sucrose consumption. Likewise, satiety signals such as leptin are not elevated with high-fat diet meals [62]. Instead, high-fat diets increase the expression of compounds involved in hunger signalling, such as galanin in the paraventricular nucleus and the orexins in the perifornical lateral hypothalamus, with overconsumption as the result [67]. At the same time, sensitivity to satiety signals is reduced in high-fat diets, as has been described for CCK [68] and leptin [69], by which overconsumption is achieved.

In summary, palatable food like fat and sucrose leads to overconsumption by triggering the reward system and by weakening the regular homeostatic appetite-regulating system [70]. Such a non-homeostatic, positive feedback circuit may seem inappropriate in the “midst of plenty”, but probably serves a physiological function under conditions when food is scarce, which has certainly been the case during the evolution of man. Occasional heavy meals involving reward mechanisms and blocked satiety mechanisms were probably essential for survival during periods of food scarcity. These mechanisms have today become a serious problem with the availability of palatable food every day, all year around.

Conclusion

It is generally accepted that obesity may start during three critical periods: (1) late fetal development with overweight at birth, (2) during the rebound period at 5–6 y, and (3) during adolescence. In infants who are overweight at birth, feeding regimens should be given to clarify that breastfeeding leads to a reduced risk of overweight compared to feeding with formula [71–73]. It should also be taken into account that regular meals which distend the stomach may influence the appetite–satiety balance in a more favourable way than snacking. One obvious advantage with snacking is that sweet breast milk immediately relieves the infant of pain and stress [74]. On the other hand, suckling induces hunger signalling, so the consequence of non-nutritive suckling by the use of pacifiers should therefore be considered. During infancy, energy requirements decrease rapidly from 120 kcal/kg body weight per day during the first months to about 100 kcal/kg body weight per day at 12 mo of age. Energy requirements then slowly decline towards puberty, being about 80 kcal/kg body weight per day at
12 y of age and around 45 kcal/kg body weight per day after adolescence.

Rebound occurs at school start when the physical activity of children declines and they start to spend an increasing amount of time watching TV and being occupied with videogames at the same time as consuming snacks. The third critical period for overweight is adolescence, when anabolic processes are stimulated.

The reasons for failed optimal weight development and poor appetite–satiety balance may be studied by following the regulatory mechanisms during these critical periods. In prospective studies, food intake in relation to growth and energy-demanding processes should be investigated. Infants who have been subjected to fetal growth restriction may develop insulin resistance, and some of them are at risk of becoming short and fat [75,76]. These infants should be studied as well as those with a high birthweight. Other studies may be started at the age of rebound. It should then be of interest to compare the BMI of children with an early rebound who become fat to those with a later rebound who remain relatively thin.

Risk factors for the development of childhood obesity have been presented in an overwhelming amount of epidemiological studies. A more physiological approach is now needed to understand the real background to overeating in childhood and its consequences.

References


[34] Huang XF, Xin X, McLennan P, Storlien L. Role of fat amount and type in ameliorating diet-induced obesity: insights at the level of hypothalamic arcuate nucleus leptin receptor, neuropeptide Y and pro-opiomelanocortin mRNA expression. Diabetes Obes Metab 2004;6:35–44.

[35] Raposoinho PD, Perroz DD, Broqua F, White RB, Pedrazzini T, Aubert ML. Chronic administration of neuropeptide Y into the lateral ventricle of C57BL/6J male mice produces an obesity syndrome including hyperphagia, hyperleptinemia, insulin resistance, and hypogonadism. Mol Cell Endocrinol 2001;185:195–204.


