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The biology of weight control

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Many clinical and commercial weight-loss programs use external controls such as kilojoule allowances to reduce energy intake. While this results in weight loss, it is not necessarily suitable for people prone to disordered eating, nor is it feasible for public health initiatives opposing obesity. In this chapter I cover the endogenous biological systems that enable humans to attain and maintain a healthy body weight – without kilojoule counting – and how genetic variations and our obesogenic environment can compromise them. These endogenous weight-control mechanisms allow individuals who don't respond well to external controls about how much to eat, to lose excess weight and keep it off, provided that the endogenous signals are heard and heeded, and the environment is conducive to doing so. These mechanisms are also suitable for community interventions.

When it comes to losing excess weight, many people utilise methods such as 'kilojoule counting' and weighing or measuring portion sizes in order to reduce their energy intake. For people not inclined to count or measure their food, structured programs are available that provide 'pre-counted' reduced energy intakes, such as specific diet menus, meal replacement programs and home-delivered meals. These are all examples of weight reducing diets in which energy intake is externally prescribed. For many people, the clear directives about what and how much to eat provided by such regimes impart knowledge about healthy foods choices and reasonable portion sizes. This is particularly important in the current obesogenic environment, where default food choices, portion sizes and the physical environment have led many adults to become overweight or obese. Weight-loss programs with externally prescribed energy intakes have helped many people to lose excess weight efficiently and – in a proportion of cases – sustainably. In fact, a recent study showed that a commercial weight-loss program involving food counting outperformed individualised attention from general practitioners in terms of helping overweight and obese adults to reduce body weight over a one-year period [1].

Despite their effectiveness for a proportion of people, weight-reducing diets with externally prescribed energy intakes are not suitable for everyone. Examples include people with

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higher or lower energy requirements than those stipulated by the diet, or those prone to disordered eating. For these reasons, in addition to the high level of support required for adherence to such diets, they are not suitable for community initiatives against obesity. In this chapter I explore an alternate solution for weight management in these people, drawing on the function of biological weight-control systems. Because these endogenous weight management systems appear to be intact in a significant proportion of people, they are potentially amenable to community-level interventions against obesity.

One size never fits all

Most clinical and commercial weight-loss programs use standardised energy intakes, with some programs offering two or three options for people with lower or higher energy requirements (eg diets providing 1200, 1500 or 1800 kilocalories per day). However, many people have energy requirements for weight loss that are different from these standardised levels, at least at times, due to intra- and inter-individual variations in factors such as body size and composition, age, sex, physical activity levels, phase of the menstrual cycle, as well as prevailing climatic conditions. This means that, for a proportion of people, weight-reducing diets with defined levels of energy intake are either ineffective or unsustainable, as outlined below.

When dietary energy intake is too high

> I found that in order to eat all of the allocated food on that diet's menu plan, I was often eating when I wasn't hungry, and I actually gained weight. (Maria, 49 years of age and 1.52 metres tall)

Losing body fat is a question of consuming less energy than the amount of energy used for basal metabolic processes, digestion, adaptive thermogenesis and physical activity. Some people's energy requirements are so low that even adherence to a 1200 kilocalorie per day diet will not result in weight loss. It is not uncommon to hear of people who started and apparently followed a weight-loss diet with a defined energy intake, only to achieve either very slow or no weight loss. While it is often assumed that the person 'must be doing something wrong', the standardised energy intakes of many weight-loss diets can be too high to produce negative energy balance in people with low energy requirements, as in older women with low muscle mass and a low level of physical activity, for example.

When dietary energy intake is too low

> With uni study, social life and trying to exercise regularly, it was not possible for me to 'diet' and 'live' at the same time. (Sabrina, 21 years of age)

A more common limitation of weight-loss diets with standardised kilojoule allowances is that people with higher energy requirements – such as younger, larger or more active individuals – can be left with inadequate energy with which to live full and active lives. A woman once told me that she often stopped going to the gym when following a commercial weight-loss program because she felt she didn't have enough energy for the vigorous workouts she otherwise enjoyed. This may be due to physical and psychological effects.

Physical effects of energy deficit

Energy deficit is known to cause adaptive responses that inhibit ongoing weight loss and which promote fat regain [2]. Emerging evidence suggests that the greater the deficit between energy requirements and intake, the greater the magnitude of these adaptive responses [3–5]. Such adaptations have been observed in overweight and obese humans and animals in response to even moderate energy restriction, and include increased appetite, reduced energy expenditure [2], a possible reduction in spontaneous physical activity [2, 5–8], and an increase in skeletal muscle work efficiency [9]. Additional adaptations include changes in endocrine status that would tend to promote the accretion of fat (particularly visceral fat) at the expense of muscle and bone, as recently reviewed [10]. For instance, energy deficit has been shown to decrease circulating levels of thyroid hormones, sex hormones, insulin like growth factor-1 and gut-derived satiety hormones such as peptide YY, in addition to increased circulating cortisol levels [10].

As larger energy deficits appear to induce stronger adaptive responses [3–5], and as the magnitude of the deficit-induced increase in appetite [11, 12] or decrease in energy expenditure [11–14] predicts subsequent weight regain, the widespread use of standardised energy intakes in weight-reducing diets could be inadvertently promoting a situation where the large get larger. For instance, a 1500 kilocalorie per day diet would produce a greater energy deficit in a woman weighing 100 kgs than in a woman weighing 80 kgs, all other things being equal. As such, the more overweight woman could be expected to exhibit a greater adaptive response to weight loss in response to the standardised diet, potentially putting her at greater risk of rebound weight gain.

Psychological effects of energy deficit

As well as having effects on physical predictors of weight regain, notably appetite and energy expenditure, energy deficit affects psychological determinants of feeding behaviour. For instance, energy restriction in rodents up-regulates hypothalamic brain expression of dynorphins [15, 16], which are endogenous opioids that induce dysphoria (an emotional state characterised by anxiety, depression, or unease). Moreover, blocking endogenous opioids with non-specific opioid antagonists such as naloxone or naltrexone has been shown to reduce binge-eating behaviour and food intake in bulimia nervosa [17] and in obese women [18]. These findings suggest that energy deficit may be contributing to changes in the brain that promote binge eating. In keeping with this, restricting energy intake to levels dictated by external factors rather than physiological needs (as in dieting) contributes to binge eating and other eating disorders in some people. Indeed, 100% of patients with bulimia and anorexia nervosa have followed restrictive diets in the past, and abstaining from such practices is part of the established treatment for eating disorders.

In light of the limitations of weight-reducing diets with standardised energy intakes, as well as the impracticality of determining energy requirements tailored to the individual needs of millions of people who need to lose excess weight, what are the alternatives?

Tapping into biological weight-control systems for individual and community solutions

Many members of the public and health practitioners alike do not realise that mammals such as humans are equipped with physiological systems that enable individuals to attain and maintain an optimum weight – without the need to follow externally prescribed kilojoule allowances – provided that the types of foods eaten are generally healthy, and provided that the endogenous hunger and satiety signals about when and how much to eat are heeded. In this and the next section I will outline how these physiological weight-management systems work, as well as the evidence that they function even in modern society, where the current obesity epidemic might suggest otherwise. An advantage of tapping into these endogenous weight-management systems is that they offer the potential for personalised solutions, where energy intake can be automatically matched to the optimal level for weight loss in each individual every day, without the need to measure actual energy requirements. These biological weight-control systems are also amenable to community interventions against obesity because – when combined with population-wide strategies facilitating healthy food and activity choices – the associated public health message could be reduced to a single instruction: eat according to your physical needs.

Pathways that prevent excessive weight gain

When an individual consistently consumes a greater number of kilojoules than that which is used by the body, the result is storage of excess energy, predominantly in the form of triglycerides (fat) in white adipose tissue. When total body energy stores exceed the level that the body defends (often referred to as the 'set point'), physiological changes that promote restoration of the set point ensue. These changes include decreased appetite, increased physical activity, enhanced energy expenditure and hormonal alterations, as evidenced below. While the appetite-inhibiting effects of energy excess are easy to override, as described later in this chapter, research suggests that these adaptive responses to energy excess occur nonetheless in up to 84% of individuals [19], making them potential targets for community-based interventions against obesity.

Positive energy balance reduces appetite

The most obvious sign of the adaptive responses opposing excessive weight gain is a reduction in appetite. Anecdotally, many people notice this after a spate of particularly heavy eating or inactivity or both (eg after holiday overindulgences), when they may not feel as drawn to as abundant or as rich foods as usual. This phenomenon has been measured in clinical trials. When healthy young male volunteers were instructed to overeat by 4200 kilojoules (1000 kilocalories) a day for three weeks and were then asked to eat *ad libitum*, they voluntarily consumed 2000 kilojoules (480 kilocalories) fewer per day than they were consuming before the experiment began [20]. Moreover, they voluntarily chose to eat foods that were lower in fat than those they normally ate [20]. Similar results have been observed in lean rodents, which exhibit spontaneous reductions in food intake in response to exposure to a high-fat diet [21], probably driven by changes in the hypothalamus of the brain as described below. Further research is required to determine whether the effect of short-term energy excess to inhibit appetite is also apparent in all people, particularly

those who are overweight or obese, as a recent study has suggested that this response may be impaired in some [22].

Positive energy balance increases physical activity

In addition to reducing appetite, energy excess increases physical activity, the amount of energy used to perform physical activity, or both [8, 9, 23], thereby helping to allay fat accumulation. Lean volunteers were asked to overeat by 4200 kilojoules (1000 kilocalories) each day for eight weeks [23]. They were specifically instructed *not* to increase the amount of exercise they did during the experiment, and they stringently maintained a low level of voluntary physical activity throughout the eight-week overfeeding period. Remarkably, the volunteers displayed a massive increase in non-exercise activities such as spontaneous muscle contractions, posture maintenance and fidgeting. In fact, the average increase in energy spent on these types of non-volitional physical activities – termed non-exercise activity thermogenesis, or NEAT – added up to 1425 kilojoules (340 calories) a day. One volunteer even burnt up 2900 additional kilojoules (700 calories) a day, which he achieved without meaning to by pacing for about 15 minutes of every waking hour. This spontaneous increase in the amount of energy expended on physical activity in response to energy excess has been confirmed in other studies in humans [9]. It is a change that has been suggested to oppose weight gain, because spontaneous physical activity in mice and rhesus monkeys negatively correlates with weight gain, consistent with human epidemiological data [24]. Not only does energy excess increase the volume of physical activity performed, it also appears to decrease muscle work efficiency in humans [9], thereby further increasing the amount of energy expended on physical activity and decreasing that available for storage.

Positive energy balance may increase energy expenditure

In addition to decreasing appetite and stimulating the amount of energy expended on physical activity, some studies have shown that energy excess leads to an increase in total daily energy expenditure or basal metabolic rate in humans [22, 25–27], albeit this has not been observed in all studies, as recently reviewed [28]. Such a change would be expected to further increase energy dissipation and help to prevent weight gain.

Neuroendocrine responses to positive energy balance

The changes in food intake, physical activity and possibly also total energy expenditure that occur in response to energy excess are likely to be mediated by associated effects on neuroendocrine status. For instance, feeding rodents a high-fat diet for eight weeks reduces expression of orexigenic peptides that promote food intake, notably neuropeptide Y (NPY) [21]. As NPY has been shown to stimulate feeding, reduce physical activity and decrease metabolic rate [2], such a change in its hypothalamic expression could contribute to effects of energy excess on appetite, physical activity and energy expenditure.

While it is not possible to measure dynamic changes in hypothalamic peptide expression in response to energy excess in humans, investigation of human body fluids or peripheral tissues provides indirect evidence of similar brain changes to those that have been

measured in rodents. For instance, overfeeding increases activity of both the hypothalamo-pituitary thyroid axis and the sympathetic nervous system in humans, as evidenced by measurements of serum thyroid hormone and catecholamine levels [29] or muscle sympathetic nerve activity [30]. Both of these changes would be expected to result from decreases in orexigenic peptide expression in the hypothalamus of the brain [10, 31], and could in turn contribute to the adaptive changes opposing weight gain in response to energy excess. For instance, induction of hyperthyroidism in rats leads to an increase in physical activity and NEAT [8, 32]. Additionally, thyroid hormones are classically known for their effect to stimulate energy expenditure by acting on peripheral tissues to directly influence cellular metabolism [33], and they have recently been shown to act in the hypothalamus of the brain to stimulate sympathetic nervous activity [34], which in turn is known to stimulate energy expenditure [35].

Changes in gut hormone secretion could also contribute to the effects of energy excess on energy intake and expenditure. Short-term energy excess in lean, overweight and obese males increases circulating concentrations of the gut-derived satiety hormone peptide YY (PYY) [36]. As PYY has been shown to reduce appetite and food intake in lean and obese humans and rodents [37–39], this change could contribute to the associated reduction in appetite seen after energy excess. Increased PYY levels could also contribute to observed increases in energy expenditure during energy excess, since PYY has been shown to increase energy expenditure in lean and obese men [40], and to decrease energy efficiency and increase core body temperature in rodents [41].

Evidence that biological weight-control systems can lead to loss of excess weight

In light of adaptive responses to energy excess such as those described above, it would be expected that eating according to individual physical hunger and satiety signals would result in reversal of past overindulgences. Energy intake would be reduced on account of the associated reduction in appetite, and increases in physical activity levels or the energy cost of physical activity, combined with a possible increase in total energy expenditure, would further facilitate loss of excess weight and restoration of the defended 'set point'. But what is the evidence that eating according to individual hunger and satiety cues – without external prescriptions on energy intake – does indeed result in loss of excess weight in lean, overweight and obese people?

Effectiveness of biological weight-control systems in lean people

In a classic overfeeding study [42], 12 pairs of lean young identical male twins were instructed to stop exercising and to overeat by 4200 kilojoules (1000 kilocalories) a day, six days a week, for 12 weeks. Every single man gained weight during the study, with a mean weight gain of 8.1 kg. As might be expected based on anecdotal observations that some people can 'gain weight just by looking at food' and others 'can eat anything they want and never gain weight', the range of weight gain was wide (4.3 to 13.3 kg), and there was a markedly greater similarity within each twin pair than among pairs with respect to weight gain. This finding shows that genetics play a significant role in determining the ability of

endogenous weight-control systems to cope with energy excess. Intriguingly, despite this wide range of weight gain among twin pairs, when the volunteers resumed their regular lives at the end of the study, *all* of them spontaneously returned to within one kilogram of their original weight within four months [42, 43]. This finding provides indirect evidence that even those individuals with a genetic propensity to gain the most weight during periods of energy excess can reverse those excesses by eating according to appetite, without the need for diets with an externally prescribed energy intake.

Similar spontaneous returns to initial body weight have been seen in men from Cameroun after four to six months of fattening by massive carbohydrate overconsumption for the traditional Guru Walla session [44]. However, a recent study of 12 lean men and six lean women showed that a four-week period of hyper-alimentation and limited physical activity resulted in increases in body weight and adiposity that were almost – albeit not completely – reversed within 12 months of return to *ad libitum* food intake and usual activity patterns [22]. It is thus likely that the homeostatic control mechanisms that contribute to reversal of energy excesses are not impervious, at least in some individuals.

Effectiveness of biological weight-control systems in overweight and obese people

It might be expected that lean young men and women would reverse energy excesses reasonably efficiently without the need for fixed energy intake prescriptions. However, evidence that homeostatic regulatory systems can also contribute to reversal of excess weight in overweight, obese or severely obese people comes from weight-loss studies involving *ad libitum* intake of a modified diet. When obese [45] or severely obese [46] men and women limited carbohydrate intake without restricting consumption of fat and protein, they lost at least as much weight after six to 12 months (~4% to 7% of body weight) as people in a control arm who consciously restricted total daily energy intake via calorie counting. Additionally, overweight or obese young men and women lost an average of ~5% of their body weight in a 12-week intervention involving the instruction to 'eat to appetite', choosing from lists of appropriate meals and snacks that would result in modification of glycaemic load and/or protein intake [47]. Similar effects on body weight are seen when the fat intake of the diet is modified without prescribing energy intake [48]. Indeed, the Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults from the National Health and Medical Research Council (NHMRC) of Australia provides evidence that low-fat diets consumed *ad libitum* can lead to weight and waist circumference losses of 2–6 kg and 2–5 cm after one year, and that these diets – if intensively monitored – may be more effective for maintaining weight loss than more prescriptive low-energy diets [48].

Potential significance for the treatment of overweight and obesity

It has been estimated that these endogenous weight regulatory mechanisms are effective in up to 84% of people [19]. This number is derived from observations that up to 84% of people tested in several independent overfeeding studies gained less weight than expected, indicating adaptive metabolic processes that dissipated part of the energy excess [19]. This means that for situations where rigid prescriptions of energy intake are impractical or contraindicated, it can still be possible for people to lose excess weight and keep it off,

provided that endogenous signals of hunger and satiety are heard and heeded, and provided that healthy foods are easily accessible and chosen. Such situations include people who eat outside the home frequently or who have a propensity for disordered eating, as well as for community interventions where it is unfeasible to mass-prescribe kilojoule allowances. There are, however, circumstances that appear to render these biological weight-control systems ineffective, at least in some people, and these are discussed below.

Factors that interfere with biological weight-control systems

There are multiple factors that interfere with the body's innate ability to defend a healthy set point weight. These include congenital disorders associated with increased appetite, such as Prader Willi syndrome, or mutations of critical genes involved in the regulation of body weight, such as leptin, the leptin receptor or the melanocortin 4 receptor. Additionally, certain medications such as cortisol and insulin can interfere with the function of endogenous weight-control systems, leading to increased hunger and weight gain unless energy intake is deliberately restrained. In this section however, I will deal with two situations that threaten the functionality of endogenous weight-control systems in the majority of – if not all – people living in obesogenic environments such as Australia. The first of these involves situations that encourage people to eat when they are not hungry, and the second involves the types of foods that are available to most people.

Environmental triggers for non-hungry eating

Availability of food in excess

In modern society, eating often occurs independently of biological hunger and satiety signals. With so many delicious, varied and affordable foods and beverages readily available, how many people stop to question whether they are physically hungry before hoeing in? We often eat irresistible foods at the moment they are offered to us. I for one find it exceedingly difficult to save a biscuit, bun or chocolate for later if a colleague brings one to my office when I am not hungry. We often eat meals simply because it is mealtime, regardless of whether or not we have an appetite. And people commonly eat out of pure boredom, joy or other emotional triggers, even in the complete absence of physical hunger. These are all examples of non-hungry eating, an everyday occurrence for most people. As such, the ability of biological weight-control systems to work effectively is compromised, even in people in whom the appetite-reducing effects of these systems are perfectly functional.

In addition to increasing the number of eating and drinking episodes per day, our environment readily offers excessively large portions at each sitting, and this appears to compromise the satiety signals that tell us when to stop eating. Research volunteers were invited to eat from a bowl of soup until they felt satisfied [49]. Unbeknown to any of the volunteers, some of them were eating soup from bowls that were slowly and imperceptibly refilling as their contents were consumed. Uncannily, these people ate a massive *73% more* than volunteers who had eaten from normal soup bowls. What is even more fascinating is that the volunteers who had eaten from the surreptitiously rigged bowls didn't feel any more

satisfied or oversatisfied than those who had eaten from normal bowls, demonstrating that we use visual as well as physical cues to determine when we have had enough to eat. This effect of larger portion sizes appears to be prolonged. When normal-weight and overweight adults were served 50% larger portions for 11 days, they ate an average of 423 additional kilocalories per day over the 11-day test period compared to an 11-day control period two weeks earlier or later in which they ate standard-sized portions [50]. This consistently increased energy intake occurred despite the fact that the volunteers reported feeling significantly less hungry and significantly more satiated during the overfeeding period than during the control period [50]. These results collectively imply that unless deliberate attempts are made to control portion sizes and heed endogenous hunger and satiety signals, then even if an individual is in energy excess with a subsequently reduced appetite, they will eat more than their physical needs dictate, and their biological weight-control systems will not have the opportunity to function optimally in the defence against excessive weight gain.

Health messages that inadvertently discourage eating according to physical hunger

It may seem obvious that our obesogenic environment pushes people to overeat when not hungry. However, even amongst people who are trying to lose weight, there is a disconnect between eating and biological hunger.

> The diet specified that you have to eat at least six times a day, as this is supposed to keep the metabolism of premenopausal women high. (Maria, 49 years of age and 1.52 metres tall)

People wishing to lose excess weight frequently seek knowledge about how to do so from the media, from books and from gyms. Unfortunately, these avenues often provide weight-loss directives that can inadvertently encourage non-hungry eating. Examples of such directives include 'eat little and often to keep your metabolism high' and 'you must eat within 30 minutes after a workout to build muscle' or 'never skip a meal'. While the importance of regular consumption of nutritious foods is acknowledged, it must be balanced with the likelihood that many people seeking to lose excess weight will have a reduced appetite due to effects of their biological weight-control systems. Encouraging eating without regard to hunger signals prevents these people from listening to the innate systems that could actually help them to lose excess weight, if heeded.

Diets high in sugar and/or fat

It is well accepted in the scientific literature that feeding rodents a diet high in sugar and fat (or high in fat) for several months results in approximately 30% of animals becoming apparently *permanently obese* [12, 51–53]. When switched to an *ad libitum* low-fat diet, these diet-induced obese rodents maintain the same elevated body weight. When placed on an energy-restricted low-fat diet, they lose weight, but once *ad libitum* access is reinstated, body weight rebounds to the elevated level. Whereas these animals would never have become obese if they had not been fed the obesogenic diet – as indicated by the fact that littermate controls maintained on the low-fat diet remain lean throughout life – the high-fat diet induces a shift in 'set point' such that a higher body weight is defended.

Genes load the gun, the environment pulls the trigger. (Quote attributed to George Bray)

Genetic blueprint is a major determinant of whether or not an individual animal will be susceptible or resistant to diet-induced obesity. However, having the genes for obesity is not enough; an individual genetically predisposed to obesity requires an obesogenic diet in order to manifest this genetic blueprint via gene–environment interactions. So what are the effects of obesogenic diets on biological weight-control systems? This question has been addressed in studies in which diets that are either high in fat, or high in fat and sugar, have been fed to animals.

Obesogenic diets induce leptin resistance

One clear effect of long-term exposure to an environment rich in dietary fat is the development of leptin resistance [21, 54–56]. The hormone leptin is a key regulator of biological weight-control systems. It is secreted in large part from white adipose tissue (body fat). Under normal circumstances, a gain in body fat leads to an increase in circulating concentrations of leptin, which in turn acts on the hypothalamus of the brain to contribute to effects of energy excess as discussed above, namely inhibition of appetite, stimulation of physical activity and enhancement of energy expenditure. However, after several months on a high-fat diet, there is a decrease in the ability of leptin to induce its effects, possibly via changes such as a decrease in the number of leptin receptors in the brain. This change in turn leads to ineffectiveness of the endogenous weight-control mechanisms, with subsequently accelerated weight gain.

Obesogenic diets induce changes resembling 'food addiction'

Constant exposure to, and overconsumption of, a high fat–high sugar diet triggers similar changes in the brain to those seen in drug addiction. These changes can override the biological weight-control systems, driving the development of compulsive overeating and excessive weight gain. When adult rats were given unlimited access to bacon, sausages, cheesecake, pound cake, frosting and chocolate (as well as normal low-fat chow) for about 20 hours a day for 40 days, they rapidly developed a preference for the high-fat foods [57]. Moreover, the rats exhibited compulsive-like feeding behaviour, demonstrated by the fact that they kept eating even in adverse conditions that normally cause rats to cease eating. At the end of 40 days, the animals had gained significant amounts of excess weight. Genetic techniques revealed that this drive to eat 'compulsively' was likely due to a decrease in the amount of dopamine D2 receptors in the striatum, a part of the brain involved in the development of addictive behaviours [57]. Dopamine is a neurotransmitter that is released in the brain in response to pleasurable stimuli such as eating, sex, or use of addictive drugs like cocaine. By acting on dopamine D2 receptors, dopamine induces changes in mood. Intriguingly, this reduction in dopamine D2 receptors in the brain is also seen in the brains of people who are addicted to drugs, as well as in people who have a body mass index in the obese range [57]. These findings may help to explain the observation that despite the presence of endogenous weight-control systems, many people overeat in our current obesogenic environment, where foods such as sausages, pound cake and frosting are easier – and cheaper per kilojoule – to procure than fruits and vegetables.

Reversibility – or not – of diet-induced brain changes that predispose to obesity

A plethora of studies such as the ones cited above unanimously show that overconsumption of a diet high in sugar and/or fat leads to changes in the brain that compromise the functionality of biological weight-control systems, at least in animals. What is not known from this research is whether such changes occur in people who have been exposed to similarly obesogenic diets for a long time, and whether any such changes are reversible in humans or animals, particularly in those with a genetic propensity for diet-induced obesity.

New evidence points to the possibility that at least some of the effects of a high-fat diet on the brain may be reversible. In one study, the severe leptin resistance seen in the hypothalamus of mice on a high-fat diet was reversed after two weeks on a low-fat diet [56]. Exercise has also been shown to alleviate the effects of a high-fat diet on the defended set point. As mentioned above, diet-induced obese rats with a strong genetic propensity for weight gain lose weight when put on a low-fat/low-energy diet, but they regain their pre-diet weight within eight weeks of *ad libitum* access to low-fat food [52]. In contrast, diet-induced obese rats that ran on a treadmill for half-an-hour a day, six days a week, regained significantly less weight than the sedentary control rats, weighing approximately 10% less, and having approximately 13% less body fat, than non-exercising controls [52]. In fact, the total body fat of the exercising rats was no different from that of lean rats that had never been obese in their lives. This beneficial effect of exercise was due to inhibition of the drive to eat rather than an increase in energy expenditure. Circumstantial evidence also suggests that effects of obesogenic diets on addiction-like changes in the brain may be reversible. Just as the low levels of the dopamine D2 receptor in the brain of people who are addicted to drugs appear to be increased upon abstinence from the drug to which they are addicted, the low levels of D2 receptor seen in postmortem brains of obese people are not apparent in brains from formerly obese people who had lost weight following gastric surgery [57]. Collectively, these findings raise the hopeful possibility that environmental and behavioural changes leading to a better diet, increased physical activity and weight loss can reverse the brain changes that compromise the effectiveness of biological weight-control systems.

More research into the potential reversibility – or not – of diet-induced brain changes is urgently needed. Of particular concern is the observation that a high-fat diet has been shown to cause epigenetic changes in the gene for leptin [58]. Epigenetic changes are changes to the DNA structure that are not encoded by the DNA sequence itself but which are nonetheless transmitted to subsequent generations. Examples include the addition of methyl groups to regions of the DNA, resulting in alterations to the expression of nearby genes. Feeding lean rats a high-fat diet resulted in methylation of DNA in the promotor region controlling the expression of leptin [58]. The link between epigenetic changes and obesity is an expanding area of research. It raises the troubling possibility that obesogenic diets not only render individuals incapable of losing excess weight, but they can also lumber ensuing generations with residual environmentally induced problems. Circumstantial evidence for this comes from the finding that the sons and grandsons of men who had been exposed to overabundant food at around the time of puberty in Overkalix, an isolated

region in Sweden, lived significantly shorter lives than the progeny of men who had not been exposed to a rare period of food overabundance in their pre-pubertal development [59].

Implications for human obesity

With these rodent diet-induced obesities in mind, it is deeply concerning to see people consuming high-fat or high-fat and high-sugar diets – with little fruits and vegetables – from an early age onwards. Is our environment robbing their bodies of the natural ability to guard against excess weight, thereby setting them and their progeny up for permanent obesity? Outstanding research questions are listed below. Sadly, we will probably have the answers to these questions when the first generation of children who have grown up almost exclusively on junk food come of age.

- Does overconsumption of an obesogenic diet induce brain changes in humans that predispose to overeating and obesity, as has been observed in rodents?
- If so, how many months or years on an obesogenic diet are required to induce such brain changes in humans?
- Are such effects of an obesogenic diet on the brain permanent, or can switching to a healthy diet, exercising and losing weight reverse them?
- What are the genotypes or epigenotypes that increase the susceptibility to diet-induced obesity in humans?
- Can we identify diagnostic biomarkers to identify children with such genotypes or epigenotypes, so that they can be protected from obesogenic diets, just as children with nut allergies are vehemently protected from nuts in the environment?

Conclusion

In modern society, the process of eating is becoming increasingly disconnected from the physical need to replenish fuel supplies. We consume highly palatable foods and beverages because they are readily available in large quantities, and lack of physical hunger is all too rarely an impediment to eating. When weight gain ensues, many people and their health practitioners resort to external directives about what, when and how much to eat. While this approach – where energy intake is determined externally – helps a proportion of people to lose excess weight and keep it off, it also results in a proportion of people eating too little or too much for effective weight loss, potentially exacerbating their overweight or obese conditions. Moreover, such methods are not suitable for everyone, especially people whose lifestyles do not afford the rigidity required to count or measure foods or eat separate meals to their family and friends, and those prone to eating disorders. Additionally, such weight-loss strategies are not suited to public health campaigns to promote healthy weight.

The body is equipped with endogenous systems to control excess weight. There is evidence that these biological weight-control systems are active in the majority of people and can enable loss of excess weight and/or maintenance of a healthy weight if the signals are heard and heeded. These biological control systems allow for individualised solutions to weight

management, because energy intake is tailored to each person's individual needs at any particular time. However, unless public health measures are implemented to improve food supply and portion sizes, and thus allow these systems to work as effectively as they are able, it will be difficult for many people to listen to the signals. This is particularly true of people with a genetic propensity for obesity. Moreover, continuation of the current obesogenic environment may lead to irreparable brain changes that make it impossible for certain people to lose excess weight, with changes potentially being transmitted to subsequent generations. While intense lobbying to change our environment via public health measures continues, benefits could be obtained now by helping people to learn to eat according to internal hunger and satiety signals. This could be achieved via commercial weight-loss programs, health practitioners, or potentially also via public health campaigns, thus enabling more people to benefit from the biological systems that naturally control body weight.

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Amanda Sainsbury is the author of two books: *The don't go hungry diet* (Bantam, 2007) and *Don't go hungry for life* (Bantam, 2011).

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