Symposium on ‘Behavioural nutrition and energy balance in the young’

Models and mechanisms of energy balance regulation in the young

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The proportion of the child and adolescent population that is in appropriate energy balance is declining throughout the developed world, and childhood obesity is a particular problem in the UK relative to other northern European countries. Assessment of the underlying causes of obesity, and the different routes to its development, may assist in the definition of successful intervention strategies. The network of peripheral and central (brain) regulatory systems that underlie energy balance and body weight and composition can, for the most part, only be approached experimentally through the study of appropriate laboratory animal models. This problem is particularly acute when the target is overweight and obesity in the young. Some of the mechanisms underlying the development of energy imbalance and specifically the onset of overweight and obesity in the young, and the metabolic health consequences of obesity, can be addressed by examination of experimental rodent models in which mutation of a single gene causes early-onset extreme obesity, genetic susceptibility to obesity is revealed in an obesogenic environment or early-life nutritional experience programmes susceptibility to obesity or metabolic problems in later life. These studies highlight genes that are essential to normal body-weight regulation in rodents and man, the impact of diet and diet-induced obesity on regulatory systems in the young and the potential sensitivity of developing regulatory systems to nutritional experiences in utero and during early life.

Obesity: Diet: Developmental origins: Diet-induced obesity

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Obesity: prevalence and causation

The prevalence of obesity continues to grow across the developed and developing world and with it the accompanying comorbidities of type II diabetes, dyslipidaemia, hypertension and CHD, which contribute to the metabolic syndrome. Many States in the USA now have obesity (BMI > 30 kg/m²) rates of > 25% (1), while in European countries obesity prevalence is in the range 10–20% for men, and 10–25% for women (2). The prevalence of obesity has increased by about 10–40% in the majority of European countries in the past 10 years, and in the UK, for example, has more than doubled since 1983. Obesity also predisposes individuals to infertility and certain cancers, and contributes substantially to health inequalities, low self-esteem and inequalities in educational and employment opportunities. Although the definition of obesity in children and adolescents may be more problematic, overweight and obesity levels currently stand in the range 15–25% in many countries (3), and are projected to rise further. Problems of overweight and obesity before puberty are frequently carried on into adult life, thereby advancing the manifestation of metabolic complications.

In view of the impact of the obesity epidemic on individuals and on healthcare resources, there is a clear need for effective interventions, be they based on lifestyle, dietary or pharmacological manipulations. Whereas obesity is ultimately the consequence of energy intake exceeding energy expenditure, with surplus energy being stored in adipose tissue, the relative stability of body weight in most healthy adults suggests that the balance between energy in and energy out is usually maintained with considerable precision, resulting in homeostasis. Informed design of interventions targeting obesity will be accelerated by
knowledge of the routes toward excessive accumulation of body fat, i.e. departure from energy homeostasis, and the mechanisms underlying the related physiological processes. Laboratory rodent models of different physiological, metabolic and disease states have been a valuable source of mechanistic data for extrapolation to the human condition for many years. This link is particularly strong in obesity research, with many studies of either patients or volunteers being derived from detailed mechanistic investigation in animal models. Accordingly, the study of developing obesity in juvenile and adolescent laboratory animals may be informative in attempting to tackle the growing obesity problem in the young human population.

Some of the mechanisms underlying the development of overweight and obesity in the young, and the metabolic health consequences of obesity, have been addressed in three distinct types of experimental rodent models: (1) single-gene mutants with early-onset extreme obesity; (2) polygenic (multi-gene) models in which genetic susceptibility to obesity is revealed in an obesogenic environment; (3) early-life (foetal and neonatal) models of nutritional programming of susceptibility to obesity. This list is clearly not exhaustive, but one that highlights key issues of energy balance in the young. Consideration of the importance and interaction of genetics and environment in susceptibility to obesity brings into play the complex molecular mechanisms that underlie the regulation of energy balance, and their sensitivity and plasticity, which will be outlined briefly.

**Mechanisms of energy balance regulation**

The reciprocal control of energy intake and energy expenditure, and thus energy balance and body composition, involves a complex network of central nervous system signalling systems including major centres in the hypothalamus, at the base of the forebrain and in the brainstem. These centres integrate feedback from the periphery related to meal processing, body composition and metabolic status, and in turn interact with higher brain centres (4). The orexigenic (feeding) and anorexigenic (starvation) populations involved in the regulation of energy balance, and of orexigenic (anabolic) and anorexigenic (catabolic) molecular substrates in these centres. The orexigenic systems increase food intake, reduce energy expenditure and give rise to positive energy balance and weight gain, whereas the anorexigenic systems have the opposite effect on each side of the energy balance equation, leading to negative energy balance. In particular, a key axis within the hypothalamus is now recognised to be that between the arcuate nucleus (ARC) and the paraventricular nucleus of the hypothalamus. The ARC appears to be the primary brain target of the circulating leptin signal (Fig. 1), and leptin-sensitive neuropeptide systems within the hypothalamus play a key role in regulating energy balance. For example, the ARC contains a number of distinct neuronal subtypes, one of which expresses leptin receptor and gives rise to leptin sensitivity. Leptin inhibits the activity of these orexigenic systems and stimulates their anorexigenic counterparts, thus forming such as glucose, amino acids and NEFA, transmit information to the brain. This signal transmission can be indirect via interaction with peripheral nerves leading to changes in firing rates or direct through actions on sensory systems within the brain itself. A number of brain sites express receptors for blood-borne hormones (e.g. the leptin receptor); Fig. 1) and by virtue of their location outwith the blood–brain barrier probably directly monitor changes in circulating concentrations. There is much complexity and redundancy in hypothalamic systems in particular, as might be anticipated given the potential implications for survival of failing to maintain at least an approximation to energy balance. Nevertheless, considerable progress has been made over the last two decades in defining the hierarchy within these signalling systems and how they interact and respond to relevant physiological challenges.

Within the hypothalamus specific neuroanatomical structures are known to be intimately involved in the control of food intake and body weight. Early evidence of such a role came from experimental or accidental lesioning and electrical stimulation studies conducted in the 1950s. More recent application of anatomical and molecular technologies has since led to the recognition of discrete neuronal populations involved in the regulation of energy balance, and of orexigenic (anabolic) and anorexigenic (catabolic) molecular substrates in these centres. The orexigenic systems increase food intake, reduce energy expenditure and give rise to positive energy balance and weight gain, whereas the anorexigenic systems have the opposite effect on each side of the energy balance equation, leading to negative energy balance. In particular, a key axis within the hypothalamus is now recognised to be that between the arcuate nucleus (ARC) and the paraventricular nucleus of the hypothalamus. The ARC appears to be the primary brain target of the circulating leptin signal (Fig. 1), and leptin-sensitive neuropeptide systems within the hypothalamus play a key role in regulating energy balance. For example, the ARC contains a number of distinct neuronal subtypes, one of which expresses leptin receptor and gives rise to leptin sensitivity. Leptin inhibits the activity of these orexigenic systems and stimulates their anorexigenic counterparts, thus forming such as glucose, amino acids and NEFA, transmit information to the brain. This signal transmission can be indirect via interaction with peripheral nerves leading to changes in firing rates or direct through actions on sensory systems within the brain itself. A number of brain sites express receptors for blood-borne hormones (e.g. the leptin receptor); Fig. 1) and by virtue of their location outwith the blood–brain barrier probably directly monitor changes in circulating concentrations. There is much complexity and redundancy in hypothalamic systems in particular, as might be anticipated given the potential implications for survival of failing to maintain at least an approximation to energy balance. Nevertheless, considerable progress has been made over the last two decades in defining the hierarchy within these signalling systems and how they interact and respond to relevant physiological challenges.

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a push–pull coordinated regulatory system, the neurones of which target the paraventricular nucleus of the hypothalamus, where receptor fields, such as the melanocortin-4 receptor (MC4-R), are located. There is strong evidence supporting the physiological involvement of these peptides in energy balance regulation (4–7) and in particular the response to negative energy balance. For example, food shortage increases neuropeptide Y and agouti-related protein gene expression in the ARC and suppresses pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript mRNA levels, leading to energy conservation while shortages persist and over-eating (hyperphagia) in compensation once food availability is restored. This discussion covers only a limited number of the hypothalamic systems involved in energy balance, and the full complexity of the regulatory circuitry is described in detail elsewhere (15).

**Single-gene causes of early-onset extreme obesity**

Extreme early-onset obesity in the human population clearly indicates the occurrence of molecular lesions that cannot be compensated for through the redundancy in regulatory signalling referred to earlier and are largely independent of the prevailing environment. The strength of the link between mechanistic animal research and equivalent human cause and effect is emphasised by the observation that all spontaneously-occurring gene mutations leading to obesity in mice find a parallel in functionally-relevant mutations in the same genes in human subjects or have identified systems in which other human genes are mutated (13). Thus, genes that are essential for normal body-weight regulation in laboratory rodents are also essential for normal body-weight regulation in human subjects. The leptin, leptin receptor and MC4-R genes exemplify genes that are essential for normal body weight in rodents and human subjects, within which mutations lead directly to early-onset juvenile obesity. Obesity in the ob/ob mouse results from a mutation in the leptin gene (5,14) and the equivalent genetically-inherited gene mutation in human subjects results in massive childhood-onset obesity (15). The effects of leptin-replacement therapy in the afflicted children are truly remarkable, with establishment of normal levels of food intake and feeding behaviour, and weight loss consisting of massive loss of body fat while lean tissue is preserved (16,17). Treatment of obese ob/ob mice with recombinant mouse leptin is similarly effective, with weight loss driven by a 75–80% reduction in food intake (9) (Fig. 2). The absence of a functional leptin signal as a result of a different genetic lesion, mutation of the leptin receptor gene, also leads to morbid obesity in both mice (db/db mouse (18)) and man (19). The critical status of the hypothalamic melanocortin system in energy homeostasis and body-weight regulation is emphasised by the obese phenotypes that result from disruption of the synthesis and processing of pro-opiomelanocortin (17,20), both of which cause reduction of the melanocortin ligand, α-melanocyte-stimulating hormone, or from loss of MC4-R function (17). MC4-R deficiency is characterised from a young age by excessive food intake, increased body fat and lean tissue accretion, and severe hyperinsulinaemia. Approximately 5% of severe childhood obesity is the result of loss-of-function mutations in the MC4-R gene (17), making this mutation the most commonly identified single-gene cause of early-onset obesity in human subjects. The MC4-R-knock-out mouse has been widely studied in the molecular dissection of the melanocortin system (21).

**Postnatal obesogenic diet**

These examples of early-onset extreme obesity contrast with the vast majority of cases of overweight and obesity in the human population in which weight gain is a gradual process that develops over decades. In contrast to early-onset morbid obesity referred to earlier, environment is now a key factor. For what has been termed ‘adult-onset’ obesity, but which now appears to be extending back into the child and adolescent population, the consensus is that relative susceptibility is engendered by overall genetic background in which small functional changes to a number of genes act in combination to favour excess weight gain. Such genetic predisposition, combined with the stable nature of the human gene pool, would implicate environmental change as a major contributory factor in the rapid increase in the incidence of obesity, including in the child and adolescent population, over the last few decades. The obesogenic environment (22,23) encompasses many aspects of modern-day lifestyles, including contemporary diets. The role of diet as a contributory factor in the majority of human obesity has increasingly led to the adoption of rodent diet-induced obesity models in mechanistic studies. These studies have employed a range of rodent species, strains and diets, and there has been discussion about the desirability of adopting both a more standardised experimental approach (24) and dietary formulations that are more relevant to human experience.

![Fig. 2. Effect of twice daily leptin injection on food intake of obese ob/ob mice. Mice were injected with leptin (△) or vehicle (○) for 7 d, with one leptin group then receiving vehicle injections for a further 6 d (▲). Values are means with their standard errors represented by vertical bars for four mice for the leptin group that received vehicle injections and five mice for the other two groups. (From Mercer et al (9).)](https://www.cambridge.org/core/terms)
i.e. diets that allow expression of preferences and palatability- and choice-driven overconsumption\(^{(25)}\). Despite the growing problem of obesity in the child and adolescent population, there have been few studies of dietary induction of obesity in juvenile rodents, and dietary interactions with energy balance systems in early life remain largely unexplored.

A strategy of feeding obesogenic diets to rats has been pursued within a week of weaning, and following an initial study in which an obligatory pellet diet was fed that was relatively high in fat and sugar\(^{(26)}\), a regimen was adopted that allowed the assessment of the consequences of providing dietary choice and both solid and liquid diets\(^{(27)}\). Feeding the juvenile Sprague–Dawley rat a pelleted high-energy (HE) diet for 5 weeks was found to give rise to animals with normal or slightly-reduced body-weight gain but increased terminal body fat and serum leptin concentration compared with controls fed the stock chow (CON)-diet. Taking into account the macronutrient composition of the HE diet, this outcome suggests a relative protein deficiency in the rapidly-growing animal leading to reduced lean tissue growth\(^{(26)}\), which, although an interesting phenotype, may not be directly relevant to the equivalent human condition. With the goal of developing a model with both additional weight gain and excess fat deposition, a test was conducted of different combinations of pelleted CON and HE diets and the liquid diet chocolate-flavoured Ensure\(^{®}\) (Abbott Laboratories, Queenborough, Kent, UK; a palatable liquid diet that provides balanced nutrition for the management of patients with, or at risk of developing, disease-related malnutrition, and employed here to induce obesity in rats through voluntary palatability-driven energy overconsumption; EN)\(^{(27)}\). Experimental groups were fed on either or both pelleted diets with or without the EN supplement, thus addressing the question of whether diets should be used that induce obesity simply because of obligatory consumption of an unbalanced combination of macronutrients or whether the capability should be built in for expression of dietary preferences, palatability-driven overconsumption and selection of an optimal macronutrient profile. Feeding these diets for 5 weeks was found to generate a range of body-composition phenotypes (Fig. 3), as a result of the dietary choices made by the animals where selection was available (Table 1), emphasising that there are different routes to obesity. With the HE and EN diets providing <15% energy from protein, the experimental groups without access to the CON diet were found to have the lowest lean tissue, but elevated body fat, whereas rats in the groups that were able to select from a combination of diets that included the CON diet chose a diet that contained ≥17% protein (Table 1). Maximum weight gain, fat and lean tissue was recorded in experimental groups for which both CON diet and EN were provided (i.e. CON+EN and CON+HE+EN groups). Provision of a choice of diets that allows the rapidly-growing juvenile rat to meet its protein requirements and also express palatability-driven overconsumption would appear to more reasonably represent the dietary exposure of the adolescent human population than a monotonous obligatory diet\(^{(25)}\), leading to the development of an overweight and obese phenotype. The extent to which issues of dietary macronutrient composition, and their consequence, can be extrapolated to children and adolescents remains to be determined, but it is not inconceivable that the macronutrient content of the diet could play an important role in the route taken to overweight and obesity. Opportunistic high consumption of foods high in energy and sweet in taste is likely to have emerged during evolution and to be subject to genetic variation, thereby contributing to susceptibility to obesity in the current environment.
In this study blood leptin levels were found to be elevated in all five experimental groups with relative obesity as a result of feeding on an obesogenic diet or diet combination, but there was also an effect of diet on leptin levels independent of adiposity\(^{(27)}\), as observed elsewhere\(^{(28)}\). As discussed earlier, there is compelling evidence of involvement of hypothalamic neurons in the development of obesity and their potential in negative energy balance, but the involvement of the same systems in counteracting positive energy balance, and their potential under these circumstances, is less well established\(^{(29)}\). Hypothalamic responses to obesogenic diets and developing diet-induced obesity are interesting in this context, and expression levels of a panel of energy-balance genes in target hypothalamic structures are being routinely assessed following dietary manipulations. In general, the outcome of these studies is consistent with the recognition of developing obesity at the hypothalamic level, in that the changes in gene expression so induced appear to be counter-regulatory\(^{(26,27,30)}\), with the most consistent changes being the down-regulation of the orexigenic genes neuropeptide Y and agouti-related protein in the hypothalamic ARC in obese rats. The additional obesogenic effect of EN when fed as a supplement to pelleted diets appears to engage some of the same energy balance systems as the solid obesogenic diet (HE), even though the pathways to obesity (i.e. energy intake, macronutrient composition) clearly differ between diets. This profile of hypothalamic gene expression as a consequence of feeding on the HE diet and/or the development of diet-induced obesity on that diet is consistent with findings from studies of young mice\(^{(31,32)}\) using high-fat diets. However, despite down-regulation by 40–50% of the expression of individual genes such as agouti-related protein\(^{(27)}\), the induced changes in these signals are apparently ineffective in countering the developing obese phenotype, suggesting that other signals, such as those generated by the reward systems in the forebrain, may over-ride the homeostatic drive. The different macronutrient requirements of rapidly-growing young rodents compared with more-mature animals appear to influence diet selection, and hypothalamic homeostatic systems may be more sensitive to energy overconsumption and consumption of a liquid diet than in older animals. The age and growth trajectory of rodents should be taken into account when extrapolating findings to children and adolescents.

### Early-life programming of susceptibility to obesity

Early-life nutritional experience is another aspect of ‘environment’ (in its broadest sense) that has an evidential link to the growing obesity crisis, with specific ontogenetic stages such as prenatal development and early postnatal life, depending on species, being particularly sensitive to programming events leading to obesity and metabolic disorders in later life. The intrauterine environment has profound effects on the development of the foetus, and epidemiological studies have revealed relationships between either poor or excessive foetal growth and subsequent development of obesity and aspects of the metabolic syndrome\(^{(33)}\). In human subjects the BMI of the child correlates more closely with that of the mother than with that of the father, supporting an influence beyond genetics\(^{(34)}\). Similarly, there is abundant evidence from rodent models that maternal undernutrition and protein restriction can induce intrauterine growth retardation, with increased risk of subsequent metabolic disorders in the offspring, while the prolongation of these manipulations into the weaning period can have severe consequences\(^{(33)}\). The linkage of these pregnancy and life-stage outcomes to the development and activity of the energy-balance regulatory systems outlined earlier is necessarily largely dependent on rodent research, but parallel mechanisms and signal perturbations can probably be assumed in human subjects. It is well established in rodents that the hypothalamic energy-balance neuronal systems begin to develop during the last week of gestation, with development continuing until weaning at 3 weeks after birth\(^{(35,36)}\). In primates development of neuronal systems takes place mainly in utero\(^{(35)}\), which suggests that in rodents and human subjects the predominant cues for the development of hypothalamic energy-balance circuits are likely to be postnatal or prenatal respectively. For example, a neonatal surge in blood concentration of the adipose tissue hormone

<table>
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<tr>
<th>Group</th>
<th>CON</th>
<th>HE</th>
<th>EN</th>
<th>Fat</th>
<th>Carbohydrate</th>
<th>Protein</th>
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<td>–</td>
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<td>12</td>
<td>65</td>
<td>23</td>
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<tr>
<td>HE</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>33</td>
<td>52</td>
<td>15</td>
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<tr>
<td>CON + HE</td>
<td>41.8</td>
<td>58.2</td>
<td>–</td>
<td>24.2</td>
<td>57.5</td>
<td>18.3</td>
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<tr>
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<td>–</td>
<td>54.9</td>
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<td>28.7</td>
<td>37.6</td>
<td>21.8</td>
<td>60.9</td>
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*The rats were allocated to six weight-matched groups and fed for 5 weeks: stock chow (CON); a high-energy diet (HE); CON + HE; CON and the liquid supplement Ensure\(^{®}\) (Abbott Laboratories, Queenborough, Kent, UK; EN; CON + EN); HE + EN; all three diets (CON + HE + EN). EN is a palatable liquid diet that provides balanced nutrition for the management of patients with, or at risk of developing, disease-related malnutrition, and is employed here to induce obesity in rats through voluntary palatability-driven energy overconsumption.
leptin appears to underlie development of hypothalamic circuits in the rodent\(^{(37)}\). In \textit{ob/ob} mice that are deficient in leptin neuronal projections from the ARC fail to develop normally, but can be rescued by neonatal but not adult administration of exogenous leptin\(^{(38)}\). In addition to the likely effect of early-life nutrition on the developing neuronal architecture of the hypothalamus, there is also evidence from rodents and sheep of functional imbalances in hypothalamic neuropeptide systems following early-life interventions\(^{(35,36,40)}\).

Whereas the evidence for programming events as a consequence of maternal undernutrition is quite firm, there is also an emerging consensus that maternal hyperglycaemia and obesity, i.e. overnutrition, may have similar adverse metabolic effects on both human and rodent offspring\(^{(33,40)}\). As the epidemic of obesity gathers pace, increasing numbers of women will enter pregnancy in an overweight or obese state, many of them with a dietary background that is high in fat and sugar. There is a need for more mechanistic modelling of these conditions, e.g. assessment of the effect of too much leptin in early life on hypothalamic development\(^{(35)}\), in order to assess the potential importance of nutritional perturbations in early life for the future health and body phenotype of the offspring. It may be possible to distinguish between the effects of diet and consequent diet-induced obesity, and to identify viable interventions\(^{(41)}\). More animal models of obesity during pregnancy are required to begin to unravel the complexities of these relationships\(^{(42)}\). A wide range of phenotypes may be affected by nutritional experiences in this early period, such as food preference\(^{(43)}\), leading to a behavioural, physiological and metabolic profile that predisposes to positive energy balance and obesity.

### Summary and conclusions

Energy balance regulation in the young is affected by the same combination of genetics and environment that impacts on this process in adult animals. However, sensitivity to environmental factors is likely to be amplified in juvenile animals as a result of the potential for influencing hypothalamic systems during the development of projection pathways, coupled to rapid rates of postnatal growth. This area is one in which the ability to transfer findings from relevant animal models to the human context is a critical issue. Perturbations in the development of hypothalamic circuits that influence communication between different hypothalamic structures, the sensitivity of those circuits to physiological challenge and the future behavioural and energetic phenotype of the animal are unlikely to be fully reversible and will contribute to the multiplicity in routes towards overweight and obesity in the young animal. In addition to the sensitivity of the developing young animal to the quality and quantity of the maternal diet from gestation through to weaning, juvenile animals are also sensitive to diet once feeding independently, and they may be more sensitive to macronutrient imbalances than an adult animal because of their rapid rate of growth. Protein availability may be especially important in the juvenile animal.

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