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Nutrition and its contribution to obesity and diabetes: a life-course approach to disease prevention?

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Whilst previously type 2 diabetes occurred in older adults, its incidence, together with obesity, has increased rapidly in children. An improved understanding of this disease pathway from a developmental view point is critical. It is likely that subtle changes in dietary patterns over an extended period of time contribute to diabetes, although this type of rationale is largely ignored in animal studies aimed at determining the mechanisms involved. Small-animal studies in which large, and often extreme, changes in the diet are imposed at different stages of the life cycle can have substantial effects on fat mass and/or pancreatic functions. These responses are not representative of the much more gradual changes seen in the human population. An increasing number of studies indicate that it is growth rate per se, rather than the type of dietary intervention that determines pancreatic function during development. Epigenetic mechanisms that regulate insulin secretion by the pancreas can be re-set by more extreme changes in dietary supply in early life. The extent to which these changes may contribute to more subtle modulations in glucose homeostasis that can accompany excess fat growth in childhood remains to be established. For human subjects there is much less information as to whether specific dietary components determine disease onset. Indeed, it is highly likely that genotype has a major influence, although recent data relating early diet to physical activity and the *FTO* gene indicate the difficulty of establishing the relative contribution of diet and changes in body mass to diabetes.

Adipose tissue: Carbohydrates: Epigenetics: Growth

A major and dramatic change in the health of children in the UK and many other developed countries has occurred over the past 10–20 years. As a consequence, primarily because of excess weight gain during early life, type 2 diabetes is now being seen in an alarming number of children[1]. This situation is not only of concern in its own right but will substantially add to the health burden of these individuals as they approach adulthood. As a result of the increased concern relating to early disease in children it has even been proposed that they are routinely placed on, for example, statins[2]. These individuals should then remain on prescription for the majority of their lives in order to ensure they do not have raised cholesterol[3]. This approach has been suggested without knowing the adverse developmental consequences statins could cause on growing children and adolescents. The present review will focus on some of the more recent findings that suggest potential pathways responsible for excess adiposity in early life and how this information may lead ultimately to sustainable strategies aimed at overcoming this health challenge.

Adiposity in early life

The recent finding that obese individuals possess approximately 30% more fat cells than lean counterparts indicates that it is not only the accumulation of excess lipid within existing adipocytes that contributes to obesity[4].

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Table 1. Summary of the plasma concentrations (mM) of the primary carbohydrates in the fetal circulation

	Glucose	Fructose	Reference
Amniotic fluid: early gestation	45	155	Jauniaux *et al.*[14]
Fetal plasma: late gestation	1·14	4·69	McGowan *et al.*[13]

What is even more striking about this finding is that the difference in fat cell number is apparent from the earliest age that measurements were made, i.e. approximately 5 years. Taken together these findings strongly suggest that the foundations for excessive adiposity are laid down during infancy and as such any therapeutic strategies aimed at preventing later obesity need to be similarly targeted. These findings are in contrast to previous work, primarily in the rat, that indicates that as there are so many fat cells present in all individuals this increase in fat cell numbers makes very little contribution to total fat mass[5], a concept that now needs re-examining.

In large animals, including sheep and pigs, the postnatal period represents the main critical window of fat growth, although the growth differs in relation to the anatomical location[6]. For example, in the neonatal pig fat is only present in the subcutaneous region[7] and is rarely found around internal organs, whilst in newborn sheep it is only present around the kidneys and heart[8]. In both species fat distribution changes substantially over the first few weeks of life, as fat is the most rapidly-growing organ through this period and is soon found throughout the body[9]. On the other hand, in term infants of normal body weight fat is present around the internal organs as well as subcutaneously, and it is the latter depot that grows substantially after birth[10]. An appreciable amount of this fat can then be mobilised during the weaning period, although this process has not been well documented. There is, however, increasing evidence that excess fat deposition can occur at this time[11] and is very likely to have adverse long-term consequences.

Metabolic precursors for fetal adipose tissue development and fetal activity

The major metabolic substrate in fat accumulation in the fetus is glucose, although in the sheep acetate also makes an important contribution[12]. In terms of other potential substrates for adipogenesis in the fetus fructose could be included, as it is the most abundant carbohydrate in the fetal circulation through gestation[13,14] (Table 1). The function of fructose in the fetus has remained elusive to date as it only contributes to approximately 20% of oxidative requirements[13]. A further reason why attention needs to be focused on the role of fructose in early life is the substantial increase in its availability within Western-style diets because of the approximately 20-fold increase in the use of high-fructose maize syrup over the past 15 years[15].

Changes in the fetal carbohydrate environment may not only impact on organogenesis but also on fetal behaviour, as glucose is the primary determinant of fetal breathing movements and as such is an indirect indicator of activity[16,17]. It could well be the case that subtle changes in early behavioural patterns may set the differences in activity, as defined by non-exercise activity and thermogenesis, that have been shown to have the potential to contribute to a gradual accumulation of adipose tissue through adulthood[18]. At the same time in the fetus the entrainment of breathing movements with sleep state and swallowing[19,20] may have the potential to influence development of the digestive system and even gut microflora. To date, this aspect of energy homeostasis has been completely ignored, but it could be important given the pivotal role that secretion of gut hormones such as oxyntomodulin and peptide tyrosine–tyrosine (both gut peptides released from intestinal enteroendocrine cells in response to a meal) have in the regulation food intake in adults[21,22]. The extent to which gut microflora may also differ between infants that are exclusively breast-fed or formula-fed remains to be established, although it is notable that the latter consume more food earlier in life and this intake is positively correlated with weight gain[23].

Diet and physical activity in childhood

It is not only the consumption of excess or inappropriate amounts of carbohydrate by the mother during pregnancy that needs to be considered but also the offspring's energy intake during the weaning period and through childhood. A striking change in dietary patterns of children between 1950 and the early 1990s is that although total energy consumption has not changed, a very different pattern of carbohydrate consumption has occurred, primarily as a result of greater sugar consumption (Fig. 1)[24]. This pattern of change has been accompanied by a dramatic change in the types of drinks consumed, with tea being replaced by soft drinks and juices. In addition, the total consumption of soft drinks is now more than double the amount of tea consumed by children in the 1950s (Fig. 1). In both children and adolescents increased soft drink consumption is further related to raised salt intake[25], thus also impacting on blood pressure control[26]. The adverse outcome in terms of overall energy balance may be even worse in children with the rise in sedentary behaviour such as watching television[27,28]. It is now recognised that the earlier a child adopts a pattern of increased television viewing then the more difficult it is to break this type of behaviour, although it can be dissociated from changes in overall physical activity[29,30]. In addition, there is a positive relationship between television viewing and consumption of dietary components advertised, including soft drinks[27].

The impact of changes in early carbohydrate consumption is complex, as early exposure to sucrose can actually reduce the motivation to acquire sucrose in young mice[31]. However, early sucrose exposure subsequently promotes weight gain in adulthood when free access is allowed to palatable energy-dense foods. Whilst it is recognised that the sugar content of some soft drinks may have been reduced in recent years by replacement with artificial

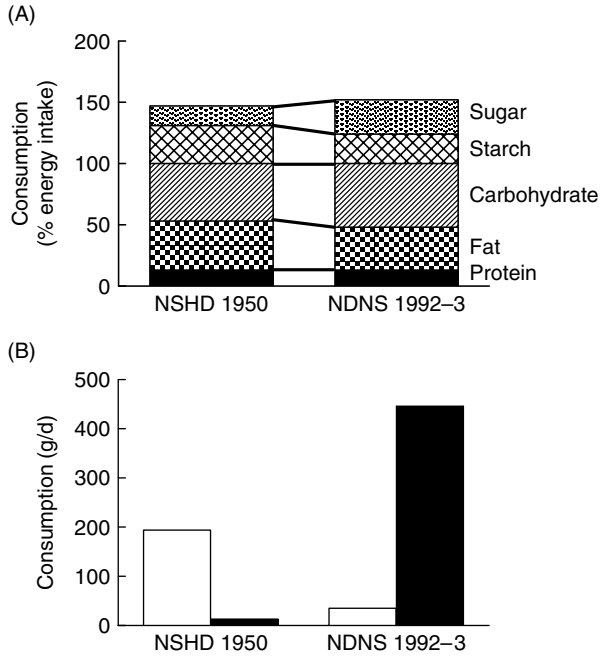

Fig. 1. Summary of the main dietary changes in children between 1950 and 1993. (A), Complete diet; (B) individual components of the diet ((□), tea; (■), soft drinks and juices). NSHD, National Survey of Health and Development; NDNS, National Diet and Nutrition Survey. (Based on Prynne *et al.*[24].)

sweeteners, it does not necessarily improve overall health. Importantly, it could even contribute to a further increase in the total carbohydrate consumption, as studies in adult rodents indicate that artificial chemicals such as saccharin are more addictive than drugs such as cocaine[32].

Genetic versus dietary causes of obesity and type 2 diabetes

Until very recently there have been no consistent reports of gene variants that influence the risk of obesity as well as predisposing to type 2 diabetes. Recent publications utilising genome-wide association studies based on a very large number of cohorts have, however, shown strong relationships between a common variant of the fat mass and obesity-associated (termed *FTO*) gene and BMI that is prevalent from as early as 7 years of age[33]. Indeed, this variant predisposes individuals to diabetes through an effect on body mass[33], a relationship that has been confirmed in a separate study based on a European cohort[34], although not in Chinese populations[35] or Oceanic populations[36]. Relative cohort size is, however, critical in determining such associations, as a minimum of 12 000 subjects are needed to show a strong relationship between *FTO* and BMI[37].

The potential divergence in response to variations in the *FTO* gene is further indicated by its widespread tissue distribution[38–40], with gene expression being greatest in the hypothalamus[40]. Moreover, in both mice[40] and rats[41] hypothalamic FTO mRNA abundance is modulated by nutritional status, but the response is species dependent; in mice starvation down regulates FTO mRNA transcription[40] whereas in rats the opposite effect is seen[41]. A number of genetic mouse models, however, indicate rapid dietary-induced obesity after consumption from 12 weeks of age of a high-fat diet in which energy intake from fat is increased 6-fold (and as such is not physiological); commencing at 6 weeks of age has no effect on *FTO* gene expression in either the hypothalamus or a range of peripheral tissues[42]. Clearly, more information is required in relation to the regulation of the *FTO* gene from a developmental point of view and how it responds to an environment of excess rather than insufficient energy supply. In this context low physical activity may amplify its association with obesity[43], although to date not all studies confirm this proposal[44].

As the number of genome-wide association studies increase both in number and scope there is an ever-increasing number of genes and loci that appear to be related to type 2 diabetes[45,46], although their predictive value for the population remains in doubt[47]. This outcome is not unexpected given the substantial number of changes in organ function that accompany type 2 diabetes, of which the main defects relate to impaired function of the pancreas together with insulin resistance[48]. To gain further insights into their relevance for glucose homeostasis such findings need to be related to changes in dietary preference and/or tissue function. For example, one genetic predisposition to sugar consumption relates to a variant of GLUT2 that is accompanied in both young and older adults by a greater intake, including that of fructose, if consumed as sweetened beverages[49] (summarised in Fig. 2). This finding is not unexpected as GLUT2 in the brain has been proposed to regulate glucose sensing, thereby having a similar function to that shown in pancreatic β-cells as well as having a primary role in regulating glucose homeostasis[50]. Within the human cohorts examined, however, there is no relationship between excess sugar intake and an overall increase in food intake or in BMI[49]. These observations are partly in contrast to findings from knockout studies in which mice lacking GLUT2 eat more of a novel powdered diet, at least in the short term, but show no difference in body weight[51]. It may be that in the human subject it is not until an imbalanced dietary pattern is attained that any pathological outcomes are manifest, such as when a dietary intake attained in which >50% total energy intake is derived from one macronutrient, be that carbohydrate or fat[52].

One pivotal factor determining diet and lifestyle from the time of conception is social class. The substantial impact that affluence has on, for example, the levels of breast-feeding and healthy adult eating patterns, as well as the proportion of the childhood population that is obese, is illustrated in Fig. 3[53]. This factor is clearly one that may be implicated in epigenetic regulation of gene action[54], which has gained substantial interest in relation to obesity and diabetes from mouse studies[55]. The translational relevance of such studies to human subjects must, however, be viewed with considerable caution, as there are far more imprinted genes in the mouse, which may make it unsuitable for disease pathway comparisons with larger mammals[56].

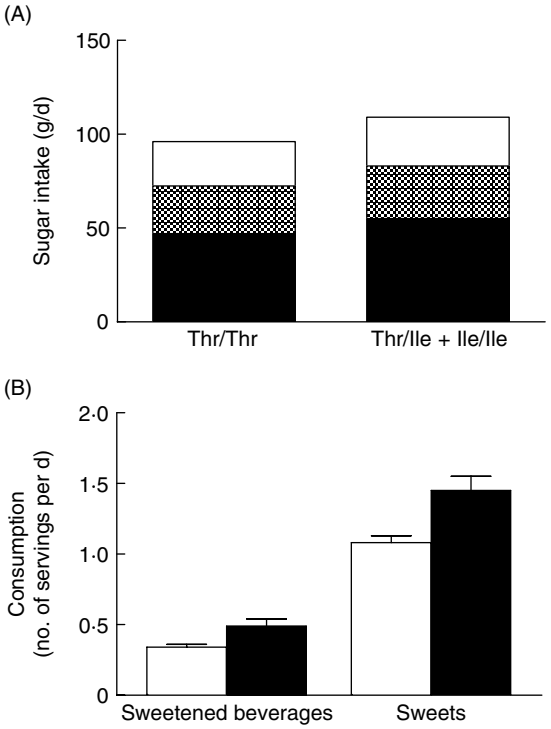

Fig. 2. Summary of the effect of a gene variant for GLUT2 on carbohydrate intake in the adult. (A) Intake (g/d) of sucrose (■), fructose (▩) and glucose (□) by Thr/Thr and Thr/Ile + Ile/Ile variants. The difference between the variants for total intake of the three sugars was significant ($P<0·05$). (B) Consumption (no. of servings per d) of sweetened beverages and sweets for the Thr/Thr (□) and Thr/Ile + Ile/Ile (■) variants. Values are means with their standard errors represented by vertical bars. The difference between the variants was significant for sweetened beverages ($P = 0·002$) and for sweets ($P = 0·0004$). (Based on Eny *et al.*[49].)

Fig. 3. Summary of the potential influence of social class on the incidence of breast-feeding, adult healthy eating (defined as the daily consumption of five or more portions of fruit and vegetables) and childhood obesity. Percentages of the population are given in relation to the best five (□) and worst five (■) performing areas of the UK[53].

Nutritional programming and epigenetic adaptations: responses to extreme dietary manipulations

The epigenome is most susceptible to dysregulation during those periods of life associated with the greatest changes in organ development and growth, i.e. embryogenesis, fetal and neonatal development, puberty and final old age[56]. For example, in the more-extreme challenge of uterine artery ligation in the late-gestation rat, which reduces uterine artery blood flow by approximately 50%[57], substantial intrauterine growth retardation occurs[58]. When these offspring are cross-fostered onto control dams they show rapid catch-up growth, an adaptation that is likely to be as important in determining the subsequent adverse outcomes as the preceding growth restriction *in utero*[59]. As adults these growth-manipulated offspring exhibit type 2 diabetes that is associated with progressive epigenetic silencing of the homeobox 1 transcription factor *Pdx1*[60], which is critical for pancreatic β-cell function and development[60]. Nevertheless, during the neonatal period the reduction in *Pdx1* expression could be reversed *in vitro* by inhibition of histone deacetylase action. Potential epigenetic effects may well be extended to a number of other tissues and cells and could include the regulation of the intracellular energy locus, as recently shown *in vitro* (using human neonatal skin fibroblasts), at least under conditions of zero or very high (i.e. 1000 mg/l) glucose concentration[61].

Further evidence that DNA methylation may have an important role in obesity comes from studies that have utilised the agouti mouse, in which a shift in coat colour from pseudo-agouti to a mottled and/or yellow appearance is accompanied by an increase in mature body weight to >40 g compared with approximately 30 g in controls[62,63]. In this model exposure to a diet that is artificially high in methyl donors as a result of an approximately 9-fold increase in choline and folic acid, approximately three times more methionine and approximately sixty times more vitamin B_{12} compared with control diets[62,64] results in a shift in the methylation pattern and thus a comparable change in the coat colour distribution[55]. This magnitude of change for each of these nutrients is extreme, especially when compared with the approximately doubling of folic acid that has accompanied dietary fortification in America[65], although re-cycling of these nutrients is very different in rodents because they exhibit coprophagia[66]. However, as the majority of these mice (i.e. approximately 90%) show a coat colour that is mottled in appearance there is actually little, if any, effect on the relative body-weight distribution, with the majority of mice continuing to have a high body weight and thus increased fat mass[55].

The recent finding that exposure of pregnant and lactating mice to the environmental oestrogen bisphenol A, which has been linked to later obesity and cancer[67], results in a very subtle shift in the number of yellow offspring but has little effect on the total number of heavy (and thus obese) mice[68]. Moreover, exactly the same shift in coat colour can be obtained by adding high quantities of methyl donors or the phyto-oestrogen genistein to the diet[68]. It therefore simply reflects the same effects both diets have in comparison with controls irrespective of the additional dietary challenge[55,69]. There is thus not convincing evidence of an 'additional protective effect' of a hypermethylating diet against the epigenetic response to bisphenol A per se[68].

It has also recently been claimed that a similar magnitude of dietary methyl donor supplementation may prevent the shift in population distribution towards an increase in body weight[70]. On closer examination of the published results it is apparent that the only change in body-weight distribution is in the F3 generation, at which time in the unsupplemented group there is a shift from 54% to 72% of all animals being >50 g compared with no real change in the methyl-supplemented group, which remained at approximately 50%. This apparent absence of a change in body-weight distribution is only because there are approximately 20% more mice in the supplemented group that all appear to have a body weight <40 g. Given that in this strain of mice the females can have up to twice as much fat as males, and thus show a much wider distribution in body weight, this result could simply be an artifact of an unequal distribution of males and females between the two groups rather than being a direct response to the excess methyl donor intake that the animals have been exposed to for three generations. Clearly, the translation of such types of extreme nutritional interventions to the human population must be considered with the utmost caution.

Conclusion

As childhood obesity and overweight constitute a global epidemic, urgent sustainable strategies are needed to prevent the accompanying diseases, including type 2 diabetes. In the UK alone obesity prevalence doubled in the 1990s, so that by 2003 three million children (30%) were considered to be obese or overweight. Of critical concern is the further recent acceleration in the incidence of childhood obesity even above that predicted, with obesity currently costing the nation approximately £7×10^9/year. It is now apparent that appropriate interventions need to be imposed as early in life as possible, for which evidence-based dietary advice linked to behavioural adaptations are pivotal.

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