Eur J Nutr (2008) 47[Suppl 3]:25–37
DOI 10.1007/s00394-008-3003-x

SUPPLEMENT

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The influence of children's diet on their cognition and behavior

Abstract The rapid growth of the brain and its high metabolic rate suggests that it is reasonable to consider whether their diet may influence the cognitive development of children. To date although there are few nutritional recommendations that can be made with confidence, there is a growing body of evidence that diet can influence the development and functioning of the brain. Several lines of evidence support the view that the diet of the mother during pregnancy, and the diet of the infant in the perinatal period, have long-term consequences. The provision of fatty acids has been the most studied aspect of nutrition, although the evidence is lacking that supplementation has long-term benefits. There is increasing evidence that the missing of breakfast has negative consequences late in the morning and a working hypothesis is that meals of a low rather than high glycemic load are beneficial. The aim is to introduce a range of topics to those for whom this area is of potential interest. Where appropriate the main themes and conclusions are summarized and attention is drawn to review articles that allow those interested to go further.

Key words breakfast – brain development – food intolerance – malnutrition

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Introduction

It's a very odd thing
As odd as can be
That whatever Miss T. eats
Turns into Miss T.

Walter de la Mare

The poem expresses the truism that you are what you eat. It follows that a good diet may help development, whereas an inadequate diet has the potential to influence adversely the rate and nature of the growth of the brain. A strong argument for considering nutrition is that particularly in the final third of gestation and the first 2 years of life, but also throughout childhood, the brain develops rapidly placing demands on the diet to provide the building blocks from which it is formed. It follows that an inadequate diet has the potential to cause damage. Therefore, the effect of the provision of food will be considered during the period of brain growth. The extent of the task is such that a systematic review of this entire area is way beyond the scope of one paper. Rather the aim is to introduce a range of topics to those for whom this area is of potential interest. Where appropriate the main themes and conclusions will be summarized and attention will be drawn to review articles that allow those interested to go further.

EJN 3003

Whether it is possible to use nutrition to further benefit those who might traditionally be thought to be well nourished, or at least consuming a diet typical of those living in affluent societies, is examined. In addition whether some children are intolerant to aspects of their diet is considered. A companion paper examines whether deficiencies of micronutrients can cause developmental problems [7].

Brain development

The human brain develops rapidly in the last third of pregnancy and the first 2 years of life. The brain weight of the newborn is about 10% of body weight, in comparison with the adult where it is only 2%. Brain weight increases with age and achieves adult weight between 6 and 14 years of age. In addition the brain is a very metabolically active organ accounting for a high percentage of total metabolic rate.

By 2 years of age the brain is about 80% of the adult weight and at one time it was believed that to a large extent brain development had ended. More recently it has become apparent that brain development continues through adolescence and even as adults the brain can adapt to changing circumstances. Adolescence is a particularly important time for brain development as more adult ways of thinking emerge: abstract thinking, deductive reasoning and the ability to solve problems. A continuing role for nutrition is plausible as although by 6 years the brain is about 95% of its final size the gray matter continues to thickening, a process that peaks around puberty. It is the gray matter of the frontal area that is particularly involved in judgment, organization and planning. Subsequently the gray matter thins as unused connections are pruned by apoptosis, that is the death of cells.

Epstein [26] surveyed brain development. Head circumference data from a dozen countries showed peaks of growth around ages 7, 12, and 15 years, that were confirmed by examination of cortical thickness, the degree of neuronal branching and the percentage of EEG energy found in the alpha-frequencies. Although a growth peak around 3 years was not demonstrated by examining brain weight and head circumference, EEG and cortical thickness data suggested that it exists. It is reasonable to assume that during times of rapid growth there are great demands placed on the provision of the nutrients that are needed for brain development. If nutrition is inadequate then the structure of the brain will be compromised. Since the 1990s there has been a great deal of emphasis on the critical importance of the last third of pregnancy and the first 2 years of life and studies of the impact of nutrition have largely reflected this stage of development. However, although the early years are important, the brain also develops during the following decades, although nutritional research has not as yet explored these later stages to any great extent.

A common idea is that there are sensitive periods in child development during which particular skills are more readily acquired. For example, Ruben [63] discussed language development and suggested that the sensitive period for phonology is up to 12 months of age, for syntax up to 4 years and for semantics until the 15th or 16th year of life. Similarly it is discussed whether there is a sensitive period during which a second language is more readily learnt [16]. It is obvious to suggest that if malnutrition prevents optimal metabolic functioning during a sensitive period of cognitive development then there may be lasting negative consequences.

Protein/energy malnutrition

If diet is influential then gross malnutrition would be expected to have adverse effects. Although it is impossible to presently fully consider the problems of gross malnutrition in the developing world, the area can be used to direct attention to the stages at which particular nutrients are likely to have their maximal impact in industrialized countries. Grantham-McGregor and Baker-Henningham [31] reviewed the evidence relating the intake of protein and energy to mental development in developing countries. They concluded that under-nutrition is associated with both short-term and longer term problems of both cognition and behavior. They found that supplementation beginning up to 24 months of age had been consistently beneficial. However, supplementation begun after this age has been found to have little or no effect, although the small number of studies limited the confidence with which this conclusion was made. For example, children in Barbados who in the first year of life were malnourished were followed up, although they had adequate birth weights and after the first year there was no subsequent lack of food. Of those malnourished in the first year 60% had attentional deficits in later life, compared with 15% in the controls [29]. Aggressive behavior was also more likely to be observed when the children were aged 9–15 years [30]. The cognitive problems resulting from malnutrition tend to be of a global nature rather than afflicting a specific aspect of cognition. However, research in this area is difficult as malnutrition tends to have a range of correlates of a social and medical nature that can themselves have adverse consequences. From a nutritional perspective many studies

have failed to separate a deficiency of energy and protein from a deficiency of micronutrients with which they are likely to be associated. To address this issue, in Indonesia Pollitt et al. [61] considered the relative importance of energy and iron. For a 12 month period children were randomly assigned to supplements that offered 1,171 kJ of energy + 12 mg iron, 209 kJ + 12 mg iron or 104 kJ alone. In these children, who were short for their age, those who received the highest energy supplements walked at an earlier age, had higher scores on the Bayley developmental scale and displayed more advanced social-cognitive and emotional behavior. It appeared that the provision of energy was more important than iron in this sample.

Malnutrition is typically associated with social and cultural deprivation such that it is difficult to distinguish the influence of one from another. To address this issue Winick et al. [75] considered Korean children who were adopted by American families at about 2 years of age and hence benefited from subsequent adequate nutrition and environmental stimulation. After they had been with their adoptive parents for at least 6 years they were divided into three groups depending on the adequacy of nutrition in the early years as judged by height when young (below 3rd, 3rd to 24th or above 25th percentile). The most poorly nourished had an average IQ of 102 with the other groups having scores of 106 and 112. School performance was similarly influenced with the malnourished performing less well. Thus although the children were randomly allocated to adoptive parents who had no knowledge of early nutrition, there were long term consequences of early malnourished irrespective of subsequent nutrition and stimulation.

However, nutrition should not be viewed in isolation as in Jamaica there was evidence of a synergistic interaction between improved nutrition and environmental stimulation [32]. In stunted children under 2 years, those who received both supplements of milk and cognitive or social stimulation were more advanced developmentally, compared with those who received neither or only one type of intervention: these advantages that were still apparent in late adolescence [70, 71].

The possible role of malnutrition on externalizing behavior in children, that is aggression, hyperactivity and conduct disorders, has also been considered. Liu et al. [43] working in Mauritius found that children who had signs of malnutrition at 3 years were more aggressive or hyperactive at age 8 years and were more likely to display conduct disorder and excessive motor activity when 17 years. The results were independent of social background and sex. There was a relationship between the degree of malnutrition and the extent of externalizing behavior: a low IQ potentiated the effect. Malnutrition was assessed by looking for clinical consequences of protein–energy deficiency or vitamin deficiency, and a low level of hemoglobin. It is difficult in such work to distinguish acute and chronic nutritional influences and the effect of macro and micronutrients.

Liu and Raine [44] reviewed the influence of malnutrition on childhood externalizing behavior and concluded that it is associated with both macronutritient (e.g., protein) and micronutrient (e.g., iron and zinc) deficiencies in both pre and postnatal periods. A speculative comment was that the long-term effects of malnutrition may be reversed by subsequent better nutrition. In particular they mention essential fatty acid supplementation although Liu and Raine [44] noted that the effects of on externalizing behavior were mixed. Benton [6], however, in a meta-analysis found that omega-3 supplementation significantly decreased hostility and anger. This consistent positive reaction to fatty acid may well reflect that the studies used similar supplements, a large dose of docosahexaenoic acid (DHA) combined with a smaller dose of eicosapenaenoic acid. Based on animal and human findings Liu and Raine [44] hypothesized that malnutrition may impair cognitive functioning by reducing the number of neurones in the brain; changing neurotransmitter functioning and increasing neurotoxicity. However, their conclusion was that only with more randomized controlled trials will it prove possible to establish the role of nutrition in externalizing behavior.

Diet in industrialized countries

Although it may seem plausible that gross malnutrition in the developing world will have negative consequences the relevance for industrialized societies is unclear. However, the possibility cannot be excluded that even in USA nutritional deficiencies may have long-term consequences. In New York, Naeye et al. [56] studied the autopsies of the stillborn and those dying within 2 days of birth, who were distinguished on the basis of parental income and social security criteria as coming from poor or more affluent families. The offspring of poor families had brains that were 15% lighter but this was true of a wide range of organs such that it was concluded that "undernutrition appears responsible for the prenatal growth retardation". In industrialized societies long-term implications of a low birth weight have been reported as it predicts disease susceptibility throughout life [3]. Although small babies rapidly catch-up in terms of weight, as adults they are more likely to become obese, develop heart disease, hypertension and diabetes. Low body weight has been proposed to be associated

with a "thrifty phenotype"; it is as if having experienced a nutritional shortage while in the womb the body is programmed to store more fat.

There are similar suggestions that body weight at birth may be associated with cognitive development. In UK, a cohort of 5,362 children born during 1 week in 1946 were tested at 8, 11, 15, 26, and 43 years of age [62]. With the exception of the heaviest, those 4–5 kg, cognitive functioning increased as a function of birth weight up to 26, but not to 43 years of age. The increase was progressive and not simply a reflection of those with very low birth weights. Adjustment for a range of possible confounding variables such a social class and parental education served only to strengthen the association between birth weight and cognition. It was presumed that birth weight was a marker for the adequacy of intrauterine nutrition during brain development. Shenkin et al. [65] reviewed the association between birth weight and intelligence and concluded that in those who were low birth weight/premature, birth weight correlates positively with tests of cognition in childhood. Overall there was a small positive association between birth weight and cognitive ability. Even though the parental social background accounted for more variance than birth weight these variables were largely independent.

More controlled data comes from the study of identical twins where the intelligence of those heavier and lighter at birth has been contrasted. Willerman and Churchill [74] found at 9.6 years that the performance IQ of the heavier twin at birth was 5.3 points greater, whereas there was only 0.4 points difference on the verbal scale. Similarly Hendrichsen et al. [33] found that identical twins, who were heavier at birth, at 13 years of age were on average 7.1 IQ points more on the performance scale of the Wechsler intelligence scale, although the verbal scale did not differ. The most likely explanation of these data is that the differences in weight at birth reflect the adequacy of nutrition in the womb.

If birth weight is associated with subsequent cognitive development then the diet of the mother during pregnancy may be influential. Mitchell et al. [52] related maternal diet during pregnancy to the risk of having a baby that was small for gestational age. Those who had children of an appropriate size for their gestational age ate significantly more carbohydrate rich food and fruit, and were more likely to have taken folate and vitamin supplements than mothers with small infants. There was also a tendency to eat more dairy products, meat, and fish. Even after adjusting for relevant factors such as smoking, maternal height and weight, fish, carbohydrate and folate intake were still associated with a reduced risk of a small for age child. Although birth weight is influenced by a range of factors, Mitchell et al. [52] suggested that during pregnancy small variations in maternal diets within the normal range are associated with differences in birth weight. Similarly Olsen et al. [57] studied 11,980 pregnant Danish women and related the weight of their child to retrospective reports of the frequency that fish had been eaten. In non-smokers, eating fish one more time a month was associated with an increase of 16 g in birth weight and 11 g of placental weight after adjusting for 19 relevant variables. In a prospective study, Olsen et al. [58] related the frequency of eating fish during the first and second trimester of pregnancy to having a preterm baby. They concluded that "never consuming fish in the first two trimesters of pregnancy was an extremely strong risk factor for preterm delivery." They postulated that *n*-3 fatty acids may improve blood flow in the placenta.

Johnson [39] reviewed the association between being born premature and cognitive and behavioral outcomes. They found a relationship between gestational age and intelligence, in particular nonverbal reasoning and simultaneous information processing. There was also a greater incidence of psychiatric disorders and ADHD in those born preterm. After reviewing the area, Bhutta et al. [14] similarly found that the cognitive scores of both preterm and term-born children were related to their birth weight and gestational age. Thus maternal diet influences the likelihood of a preterm birth and hence subsequent cognitive and behavioral development. The possibility exists of influencing the cognitive development of the child by improving the diet of the pregnant mother although precise details of the optimal diet need to be established.

The diet of infants

In the industrialized world breast-feeding is probably the topic that has been most often studied, resulting in many reports that it is associated with better cognitive development [2]. However, as the decision to breast feed is more common in mothers who are better educated, more affluent and of higher intelligence it is difficult to distinguish the provision of mother's milk from a range of environmental benefits.

As premature infants are fed initially by tube it is possible to compare, at a critical stage for brain development, the influence of milk of different compositions on subsequent development. When two groups were compared, those children whose mothers expressed milk to be administered by tube were more developmentally advanced at 18 months, compared with those consuming a cows milk based formula [53]. As the decision to express milk may reflect more

general attitudes towards child-rearing, and children were not allocated randomly to their diet, the findings are difficult to interpret. In addition although it has been suggested that the higher levels of fatty acids in human milk are beneficial, it is difficult to exclude a role for other factors, for example, the transfer of the mother's antibodies to the child. However, a meta-analysis concluded that after adjusting for appropriate confounding variables, breast-feeding was associated with better cognitive development than formula feeding [2]. Even in those aged 10–15 years there was a significant difference of over three IQ points, although the benefit was only significant in those who had breast-fed for more than 8 weeks.

More recently more cautious conclusions have been suggested. Jain et al. [38] distinguished studies depending on their methodological rigor. Of the 40 studies they identified, 68% had concluded that breastfeeding promotes intelligence. Many studies, however, had methodological flaws. Only two considered full-term infants and met the methodological criteria they demanded. Of these one concluded that the effect of breastfeeding on intellect was significant, and the other did not. They found that although the majority of studies concluded that breastfeeding promotes intelligence, the evidence from higher quality studies was less persuasive. Recently attention has been drawn to the importance of the socio-economic correlates of the decision to breast-feed [79]. Der et al. [22] considered 5,475 children who were part of the 1979 US national longitudinal survey of youth. Before adjusting for confounding variables breast feeding was associated with an increase of around four points in mental ability on the Peabody individual achievement test. However, the mother's IQ was more predictive of breastfeeding status than race, education, age or poverty. When the effect of mother's intelligence was taken into account breast feeding had little or no effect. This finding illustrates the importance of measuring maternal intelligence rather than proxy measures such as maternal education or social background and should be included in future studies.

Fatty acids

Irrespective of whether breast feeding is or is not beneficial, the high levels of fatty acids in human milk has attracted attention to the extent that artificial formulae, supplemented with sources of long-chain polyunsaturated fatty acids, have been marketed. The *n*-3 fatty acid DHA and the *n*-6 fatty acid arachidonic acid (AA) are the major long chain polyunsaturated fatty acids in the brain. As these fatty acids are incorporated into the brain during its growth spurts, the nature of nutrition at this stage has attracted attention. After adipose tissue the brain is the organ richest in lipids, to the extent that they represent about 60% of its dry weight and more specifically they make up 80% of nerve cells. Fatty acids play an important structural role in cell membranes where unsaturated rather than saturated fatty acids are associated with a more fluid membrane, such that communication both from and to the cell is facilitated [15]. Yet *n*-3 and *n*-6 fatty acids are essential, that is as the body is not able to make them they must be supplied by the diet. The possibility that a diet with a limited supply of fatty acids may impact on child development has, therefore, attracted attention.

In 11,875 pregnant women Hibbeln et al. [34] related the consumption of seafood, a rich source of essential fatty acids, to the subsequent development of their child. A greater intake of seafood during pregnancy was associated with greater pro-social behavior, better fine motor control and social development scores and higher verbal intelligence at 8 years of age. A lower intake of seafood during pregnancy was associated with a higher risk of suboptimal development. The findings of this study are controversial as in the USA women are advised to limit their seafood intake during pregnancy to 340 g/week, to reduce the risk of contamination with neurotoxins. However, it was claimed that the findings reflected beneficial effects in those with maternal seafood intakes of more than 340 g/week. There are many potentially confounding variables, e.g., fish consumption is greater in the more affluent and better educated, although the effects persisted when 28 potentially confounding variables were considered. The suggested mechanism was the level of the intake of fatty acids that was related to the amount of fish eaten. A more certain conclusion is offered by studies that used double-blind trials to compare infants fed with a cows milk based formula, that either has or has not been supplemented with fatty acids.

McCann and Ames [50] concluded that evidence from the study of animals suggests that changes in brain concentrations of DHA are positively associated with changes in cognitive or behavioral performance. However, additional information was required before concluding that infant formulae should be supplemented with DHA. In a Cochrane review, Simmer and Patole [66] reported that most studies did not find a significant difference in visual acuity between those who received fatty acid supplements and controls. Similarly most of the trials that have used the Bayley scales of infant development at 1 or 2 years of age showed no effect of supplementation. In addition most trials reported no significant effect of supplementation on the growth of preterm infants.

Eilander et al. [25] reviewed more recent intervention studies and considered various groups. With term infants and children over 2 years of age they could find hardly any evidence for an enhancement of cognitive functioning associated with fatty acid supplementation, although there was consistent evidence of a beneficial effect on visual development in the first year of life. However, with preterm babies there is evidence from two studies of a beneficial effect of early supplementation on cognitive development in the first year. Fatty acid supplemented boys but not girls had significantly higher mental development scores at 18 months [28] and similarly [21] found higher mental and psychomotor development at 18 months in preterm infants who were supplemented. Eilander et al. [25] also found suggestive evidence that the administration of DHA to pregnant and/or lactating women benefits the mental development and longer-term cognitive functioning of the child, although the effects were small, inconsistent and tended to occur when measured at some ages but not others. As an example Lauritzen et al. [42] gave Danish mothers, with a fish intake below the population median, either fish or olive oil for the first 4 months of lactation. Vocabulary at 1 year was lower in the children of mothers taking fish oil although there were no differences at 2 years of age. Word comprehension at 1 year was inversely associated with the levels of erythrocyte-DHA at 4 months. Thus at one age at least this study found supplementation to have a negative impact. After acknowledging the inconsistencies, Eilander et al. [25] concluded that the evidence was promising yet inconclusive. However, to date there is little evidence of a beneficial influence of fatty acids when they are given to full-term infants or older children. The possibility exists that more reliable effects may be demonstrated if the dose and composition of the fatty acid supplements are systematically considered.

Premature infants

Methodologically some of the best data have been obtained from the study of premature infants who were fed initially by tube. Lucas et al. [46] randomly allocated premature children to a traditional cow milk based formula or one enriched with protein, vitamins and minerals. At 18 months those who had consumed the enriched formula showed more advanced social and psychomotor development. At 8 years of age boys but not the girls had significantly higher verbal intelligence scores [45]. It appears that early nutrition can have long-term consequences. Boys fed the standard formula had a 12.2 point disadvantage in intelligence. Four weeks was the median time that the formulae had been administered. This research programme demonstrates the important point that the effects of diet may not emerge for many years and it is important that follow up studies are conducted over extended periods to ensure that effects are not missed.

Perhaps the most convincing evidence that the nature of nutrition during brain development can be influential comes from brain imaging studies of the children at 16 years of age in the prospective study of Lucas. As the caudate nucleus may be especially vulnerable to early environment [1], Isaacs et al. [36] used MRI to estimate the volume of this area of the brain and related it to measures of intelligence. In preterm boys, but not girls, those who had consumed an enriched formula after birth had a larger caudate nucleus and higher verbal intelligence, compared to those who had consumed the standard infant preterm formula. These findings offer a possible neural basis for the effects of early diet occurring predominantly in males [45].

These studies of premature infants strongly suggest that the nature of early nutrition can have long-term consequences. It is, however, unwise to uncritically generalize such findings to full-term infants whose brain development will be more advanced. Similarly without a consideration of a range of dietary supplements it is impossible to identify the critical nutrients and the appropriate dose.

Meals and cognition functioning

As well as affecting the architecture of the brain, nutrition can also potentially influence functioning from moment to moment. Although the adult brain represents only 2% of body weight it is responsible for 20% of basal metabolic rate. However, Chugani [20] reviewed the evidence that brain tissue from a child uses more glucose than if it came from an adult. From birth to 4 years of age the rate of glucose utilization by a given weight of brain tissue increases markedly, to the extent that by 4 years it is twice that of the adult. In the neonate the brain is responsible for 44% of the basal metabolic rate [23]. A high rate of glucose utilization remains until nine to ten years. The cerebral metabolic rate then declines to reach adult values by 16–18 years of age. To achieve its role as the most metabolically active organ in the body the brain needs to be continually supplied with glucose, its basic fuel, as well as the range of other nutrients that facilitate metabolic processes. The question arises as to whether the nature of the diet and the pattern of meal consumption may influence psychological functioning in the hours after eating, by acutely influencing the supply of nutrients.

Carbohydrate and breakfast

The short-term reaction to the composition of meals and meal patterns is attracting increasing interest. When Pollitt and Mathews [60] reviewed the literature on the influence of breakfast on cognition they found that no definite conclusion was justified. They did, however, find that the data strongly suggested that omitting breakfast interferes with cognition and learning, particularly in children who were nutritionally at risk. In fact there have been surprisingly few studies of the effect breakfast, as opposed to fasting, in children living in industrialized countries. There have been even fewer studies of the impact of the composition of the meal.

In 9 to 11-year-olds breakfast rather than fasting enhanced cognitive performance 1 h after eating [48]. After boys, aged 9–12 years, had consumed confectionery rather than a noncaloric snack for breakfast Busch et al. [18] found that a vigilance task was significantly improved after an hour. Memory was better in 12-year-olds eating breakfast cereal, rather than fasting, but only for half an hour [69].

There has been little attempt to establish the optimal nature of breakfast. In Sweden 10-year-old school children who ate larger breakfasts exercised for longer in a morning gymnastics class and displayed better verbal fluency [78]. In 12-year-olds, after eating breakfast cereals the decline in attention and memory over the morning was less than if they fasted or consumed a glucose drink [73]. Mahoney et al. [48] compared oatmeal and a ready-to-eat cereal that offered similar levels of energy but differed in macronutrient composition. Boys and girls aged 9–11 years showed enhanced spatial memory and girls showed improved short-term memory after consuming oatmeal. Younger children had better spatial memory and better auditory attention, and girls exhibited better short-term memory after consuming oatmeal. Although not specifically manipulated it was speculated that differences in the speed that carbohydrate was digested might have influenced cognition. A breakfast containing more slowly digested carbohydrate will gradually release glucose into the blood over a longer period [48]. Ingwersen et al. [35] found that breakfast cereals differing in their glycemic response influenced the cognitive performance of children. The low glycemic meal slowed and reduced the decline in attention over the morning.

The idea that children benefit from the consumption of a breakfast with a low glycemic load can account for much of the literature. In young adults two breakfasts were compared that contained a similar amount of carbohydrate that differed in the speed with which they released glucose into the blood [12]. A slower release of glucose was associated with better memory in the late morning. Similarly when breakfasts were compared, designed to offer various combinations of high and low levels of carbohydrate, fat and protein, better memory was associated with better glucose tolerance and the consumption of meals that more slowly released glucose into the blood [54]. Again when various amounts of carbohydrate were combined with various amounts dietary of fiber a slower release of glucose influenced cognition [55]. Benton et al. [11] over a period of a month studied the effect of isocaloric meals designed to differ in the glycemic load (GL) on the school performance of children aged 6–7 years. A low GL breakfast was associated with better memory, better sustained attention and spending more time on task. In regression equations the GL rather than other aspects of the macronutrient composition tended to predict behavior.

Snacking

Although it is often assumed that there is virtue in avoiding eating between meals, in many people it is the norm. As a frequent reason given for snacking is to decrease fatigue, or sustain attention, it is surprising that this dietary style has been little considered. In adults there are reports that eating candy decreased tiredness in the afternoon [68] and that a snack improved memory and attention in the afternoon but not the morning [40]. After 1 hour on a driving simulator the consumption of chocolate resulted in more careful driving in the second hour [67]. In 7-year old children Benton et al. [9] found that the ability to sustain attention improved and there was a decreased reaction to frustration when a glucose containing drink, rather than a placebo, was consumed in the afternoon.

In young adults, a breakfast high in carbohydrate (50 g) was associated with poorer mood in the late morning, a reaction that was not observed if a midmorning snack was eaten or a smaller breakfast (10 g carbohydrate) consumed [13]. Only recently has there been any study of the effect of the size of a child's breakfast and its interaction with a subsequent snack. In nine year old British children Benton and Jarvis [10] considered the influence on school work of the size of breakfast and whether a midmorning snack had been consumed. Those who had eaten a small breakfast, on average 61 kcal, spent significantly less time attending to their work than those who had eaten larger meals, on average 210 or 270 kcal. The adverse effect of a small breakfast was reversed by the consumption of a midmorning snack.

Glucose provision to the brain

Given the importance of the brain and the homeostatic mechanisms that ensure the provision of glucose [5], it may appear improbable that the nature and scheduling of meals influence its functioning. Naturally there is no measure of the brain glucose levels of children after eating particular meals. However, the use of positron emission tomography indicates in general terms the way that the brain uses glucose. When faced with cognitive demands glucose utilization increases selectively and rapidly in those areas associated with the processing of particular information. A change in blood flow results from capillary recruitment with an associated provision of glucose. As the blood–brain barrier does not limit the entry of glucose it has been often suggested that the provision of glucose does not limit functioning. However, the important question is not whether glucose crosses the capillary wall quickly enough but rather whether capillary recruitment is always sufficient to direct sufficient blood to metabolically active areas and to establish stores of glucose that were available prior to meeting a demand. The traditional model of the supply of glucose to the brain relies on two basic assumptions. Firstly that the level of glucose is the same throughout the brain; that is the brain can be treated as one compartment. Secondly that the level of glucose does not vary; that is the capacity to transport glucose exceeds the demands placed upon the brain. These assumptions create considerable problems when trying to understand reports that the administration of glucose, both peripherally and directly into the brain, enhance cognition [5]. However, both these assumptions about the provision of glucose have been questioned.

For many years, it has been assumed that there is a single compartment for glucose in the brain with a concentration that was stable and hence under normal circumstances did not limit neural activity [47]. If this model was correct then the provision of glucose to the brain should not influence its functioning. This view has been challenged by reports that the concentration of brain glucose varies from brain area to brain area, and from time to time within a particular area of the brain. It is becoming clear that in resting animals the levels of extracellular glucose vary with the area of the brain considered [51]. Secondly behavioral testing has been found to cause fluctuations in extracellular glucose levels that appear to be localized to those areas specifically involved in processing a particular task [5]. For example, McNay et al. [51] measured the levels of extracellular glucose in both the hippocampus and striatum while rats were learning a maze. At rest the level of glucose in the striatum was 70% of that in the hippocampus. When learning a maze the level of glucose declined by 32% in the hippocampus but it increased by 9% in the striatum. The fall in hippocampal glucose reflected the cognitive load as the level of extracellular glucose in the hippocampus declined by 32% when rats learned a four-arm maze but only by 11% when learning a simpler three-arm maze. These findings are consistent with the decline in brain glucose being a reflection of the metabolic demands placed on the brain. It was particularly interesting that a peripheral injection of glucose both prevented a fall in extracellular glucose in the hippocampus and enhanced maze learning. However, the administration of glucose did not change the extracellular concentrations of hippocampal glucose when the animal was at rest. It seems that during learning the demand for glucose by the hippocampus did not match its supply. The ability of a glucose supplement to influence the levels of extracellular glucose in the brain suggests the possibility that the nature of diet could have a similar effect.

Adverse reactions to diet

Although usually we consider the positive reactions to nutrition there are suggestions that on occasions the reaction can be detrimental.

Feingold diet

Although for many years the Feingold diet has been largely ignored by science it is still recommended by some self-help groups. The diet was based on the assumption that salicylates, chemicals in food with a similar structure to aspirin, and synthetic additives that are commonly added to processed foods, cause hyperactivity. The yellow dye tartrazine was specifically implicated [27]. The Feingold theory stimulated a great deal of research, although reviews concluded that the modification of diet was not an effective intervention for hyperactivity [41, 72]. By chance later well-designed studies proved to be powerful tests of the Feingold hypothesis. Foods low in salicylates include meat, fish, shellfish, milk, cheese, eggs, wheat, rye, oats, barley, rice and some fruits and vegetables. Foods high in salicylates include most herbs, spices, some fruit and vegetables, nuts, yeast-rich products and many processed foods. Although testing the effect of the Feingold diet was not the aim of the study, Egger et al. [24] found that many children responded negatively, under a double-blind challenge, to the foods low in salicyclates that formed the core of the Feingold diet. With hind-sight it seems that Feingold views failed to reflect the complexity of nutrition and

physiology by paying too much attention to one group of chemicals, the salicylates.

Food intolerance

There is, however, evidence that some children respond adversely to particular items of food with behavioral consequences; reactions that may occur for many reasons. Food intolerance is the generic term used to include a range of mechanisms that generate negative reactions [59]. A food can be malabsorbed due to an enzyme deficiency; naturally occurring chemicals in food, such as histamine and tyramine, can cause an adverse reaction; an allergic response involves the immune system. In addition a reaction to food for psychological rather than biological reasons has been termed "food aversion". It is not uncommon for people who are certain that they respond adversely to diet, to find that when tested under double-blind conditions they fail to react. A risk is that many children have been taught to respond adversely to food, a reflection of the false but strongly held belief of their parents' that diet is the cause of their behavioral problems.

Food intolerance and hyperactivity

It has become apparent that the study of single food items reflects too simplistic an approach. Benton [6] reviewed studies of food intolerance that consider simultaneously possible negative reactions to a wide range of food items. These studies restricted children with a history of hyperactive symptoms to an oligoantigenic diet (few foods). Other foods were then reintroduced one at a time and if there was no negative reaction they were retained in the diet. Critically those foods to which a negative reaction had been observed were then tested using a double-blind procedure. Children produced idiosyncratic responses with several dozen foods proving to be a potential problem. For example, Egger et al. [24] found that the most common substances to which children responded were the artificial colorant tartrazine and the preservative sodium benzoate, to which 79% of their sample responded. However, no child was sensitive to these additives alone and it was not possible to single out additives, or particular foods, as a unique or universal cause of problems. Cows milk caused an adverse reaction in 64% of children; other foods that were a frequent problem were chocolate (59%), grapes (49%), wheat (49%), oranges (45%), cows cheese 40% and hens egg (39%). Benton [6] used meta-analysis to integrate the findings of five double-blind placebo controlled studies of the impact of food intolerance in hyperactive children. The standardized mean difference was 0.80 of a standard deviation (95% CI, 0.41–1.19); there were significantly fewer symptoms of hyperactivity when the children consumed a placebo meal than when they ate what for them was a problem food.

It is important to develop a means of identifying those children who are likely to respond negatively to specific food items. For example, Carter et al. [19] found that 85% of those who responded were more likely to crave foods compared with 30% of nonresponders. Those who responded to specific food items were more likely to have previously been placed on a diet by their parents; this was true of 90% of those who responded and only 6% of those who did not respond to dietary manipulation. Boris and Mandel [17] found that atopic children with attention deficit hyperactivity disorder were more likely to display an adverse reaction than those who were nonatopic. As the studies of food intolerance have tended to recruit children from clinics using a dietary approach, it is inevitable that the responses considered in the meta-analysis [6] reflected a self-selection by parents who already suspected that diet influenced the behavior of their child. The important question is the frequency with which such problems occur. Is it the majority or a minority of children displaying behavioral problems for whom diet is a problem? Findings obtained from children whose history suggests that they have a dietary problem should not be uncritically generalized to all children, or even to all children with behavioral problems.

These conclusions do not offer easy solutions. It is easy to imagine eating of up to thirty different foods per day with many processed foods containing scores of ingredients. Not all these ingredients are likely to cause food intolerance but it makes the problem food difficult to distinguish. The existing controlled trials make plausible the suggestion that some children have unrecognized food intolerance that result in behavioral problems. We urgently need to develop the means of distinguishing children who have such problems and the means of distinguishing the foods to which an individual reacts.

Sucrose

As it is a frequent assumption in the general population that sugar adversely influences the behavior of children the topic is considered. Meta-analyzes of double-blind studies, that have examined the impact of sucrose on the behavior of children, have produced no evidence that it has an adverse influence [8, 77]. For 3 weeks in a double-blind trial Wolraich et al. [76] provided families living in their own homes meals that were sweetened in various ways. They

found no differences in behavior when meals containing sucrose or artificial sweeteners were consumed. Benton [8] reviewed various mechanisms by which sucrose could possibly influence behavior. The first was food intolerance. As discussed below there are dozens of foods to which an adverse reaction has been demonstrated in children with hyperactive symptoms. However, sucrose is not near the top of the list of problem foods and others, such as wheat and dairy products, are a greater concern. A second possible mechanism is hypoglycemia. Although there is evidence that a tendency to develop low but not necessarily hypoglycemic levels of blood glucose is associated with irritability and violence, sucrose is not the predominant cause of swings in blood glucose levels.

Additives

Although there were several dozen food items that generated an adverse reaction, Egger et al. [24] found that the artificial colorant tartrazine and the preservative sodium benzoate were the substances that most commonly induced a response. Yet early reviews of the influence of additives on hyperactivity and related disorders concluded that the nature of diet and the consumption of additives did not influence hyperactive behavior [41, 72]. Those favoring the approach, however, noted that little more than 10 out of over 3,000 additives have been considered in such studies, and often at levels lower than those consumed by a typical child. Reactions were said to have been monitored for too short a time and to have failed to control for nutritional status. In contrast more recent reviewers have suggested that additives can have an effect [37, 64]. Using meta-analysis, an effect size was found of 0.28 (95% CI, 0.08–0.49) that fell to 0.20 (95% CI, 0.01–0.41) when the smallest and lowest quality trials were excluded [64]. It was concluded that the administration of additives in well designed trials caused behavioral problems. It is interesting to compare the meta-analysis of the effect of additives with the meta-analysis of more general food intolerance. The consideration of additives and food intolerance together [6] resulted in an effect size four times greater than when only food colorings were considered [64]. It is relevant that Egger et al. [24] never found a child who responded only to additives and never found a child who responded to only a single food item.

Again it is important to distinguish the general population from a self-selected group of children whose parents believed they responded to food: children taking part in trials of additives have been typically those whose parents suspected that there is a problem. In this context it interesting that Bateman et al. [4] looked at a population sample of children in their fourth year, who were assessed for hyperactivity and their reaction to a series of allergens in a skin prick test. Four groups of children were distinguished, those with high and low hyperactive symptoms and high and low atopy (tendency to develop the allergic diseases). They consumed fruit juices to which the artificial colors sunset yellow, tartrazine, carmoisine, ponceau, and the preservative sodium benzoate, either had or had not been added. Parental ratings of children's activity were higher when the children had consumed the additives rather than the placebo. A response was found in all groups of children: it did not matter whether or not the child was hyperactive, or whether or not the child had an allergic tendency. However, some have questioned the finding as differences were not detected in the clinic or by supposedly more sensitive psychological tests. Critically, the finding was subsequently replicated. In a double-blind placebo-controlled trial artificial food color and additives affected childhood behavior [49] as judged by a global measure of hyperactivity. The finding was obtained in both 3 and 8/9-year-old children from the general population. However, the use of a cocktail of additives makes it unclear which were having an influence and whether combinations rather than single substances may be influential. As this is the first study to consider a nonclinical community based sample the findings are of considerable interest.

Discussion

Broadly there are two ways in which diet can potentially influence the brain and hence cognition. Firstly the structure of the brain can be influenced, particularly at times of rapid growth, with the possibility that its structure will be influenced. Secondly the provision of energy, or the efficiency with which it is used, may have a short-term influence on the way a child functions.

A fundamental question is whether there are critical or sensitive periods in development when we need appropriate nutrition. Is there a stage when nutritional deficiency will cause damage that cannot be fully reversed by a subsequently better diet? If there are critical periods of development their identification is vital so that adequate nutrition can be targeted to prevent long-term damage. From the developing world there is growing evidence that protein/energy malnutrition during infancy can cause lasting damage [31]. In industrialized societies the influence of the mothers diet on the weight of the new-born [52], and the influence of the weight at birth on subsequent

development [62], suggests the need to further consider the diets of pregnant mothers and of full-term infants in the perinatal period. In particular the well designed studies of Lucas suggested that in the perinatal period nutritional status can have long-term implications [36, 45, 46].

Although these findings support the general principle that diet is important much is as yet unclear. To what extent are these reports only typical of premature infants whose brains are at an early stage of development? It should be recalled that the effects were apparent in males rather than females. The enriched diet used contained 40% more protein and 18% more energy in addition to a range of vitamins and minerals. Given that the composition of the enriched formula in the Lucas study was an educated guess it would be extremely fortunate if it could not be improved by adding additional nutrients or systematically considering the doses of those that were included.

Secondly, we need to consider the short-term influence of meals. Does the composition and patterning of meals influence the ability of a child to concentrate and benefit from their schooling? Traditionally the suggestion that the short-term provision of energy would be influential would be greeted with scepticism. In those whose diet provides sufficient energy a series of homeostatic mechanisms are thought to ensure that the supply of glucose to the brain does not, under normal conditions, limit functioning [5]. However, irrespective of the underlying mechanism there is increasing evidence that eating breakfast as opposed to fasting [48, 73], eating meals of a different nutritional makeup [6, 10, 35] and the consumption of snacks [9, 10] can influence the cognitive functioning of children.

After this brief review what messages can be taken away? Firstly the rapid growth of the brain and its high metabolic rate suggest that we should consider the potential impact of diet on child development. The diet provides both the building blocks from which the brain is constructed and the fuel that generates its activity. At the very least it is a topic that needs to be addressed in the hope that it may prove possible to offer dietary advice, or develop novel food products, that will aid the development of children.

In developing countries there is increasing evidence that malnutrition has negative effects that may be long-term if it occurs during the early rapid period of brain development [31]. At least in preterm babies the diet of the neonate can have lasting implications for brain development [36] and hence cognitive functioning [47, 49]. In full-term infants the association between birth weight and subsequent development [62], and the influence of maternal diet during pregnancy on birth weight [52, 57], suggests that the diet of the mother during pregnancy may have lasting consequences for the intellectual development of the child. Thus, there are several lines of evidence that suggest that birth weight predicts cognitive development such that attention should be directed to nutrition during pregnancy and in the perinatal period.

There is growing evidence that nature and patterning of meals can have implications for functioning in the short-term. The importance of the glycemic loads of meals is a working hypothesis in the area; a perspective that leads to the expectation that there will be interactions between the timing and composition of meals and snacks.

Acknowledgments The authors would like to thank the reviewers Bonnie Kaplan and Joachim Westenhöfer for their useful comments and discussions.This work was commissioned by the Nutrition and Mental Performance Task Force of the European branch of the International Life Sciences Institute (ILSI Europe). Industry members of this task force are Barilla G. & R. Fratelli, Coca-Cola European Union Group, DSM, Groupe Danone, Kraft Foods, Nestlé, Südzucker/BENEO Group, Unilever and Wild Flavors. For further information about ILSI Europe, please call + 32-2-771.00.14 or email: info@ilsieurope.be. The opinions expressed herein are those of the authors and do not necessarily represent the views of ILSI Europe.

Conflict of interests The author has no financial or other interests that might conflict with the views expressed.

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