Nutritional influences on cognitive function: mechanisms of susceptibility

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The impact of nutritional variation, within populations not overtly malnourished, on cognitive function and arousal is considered. The emphasis is on susceptibility to acute effects of meals and glucose loads, and chronic effects of dieting, on mental performance, and effects of cholesterol and vitamin levels on cognitive impairment. New developments in understanding dietary influences on neurohormonal systems, and their implications for cognition and affect, allow reinterpretation of both earlier and recent findings. Evidence for a detrimental effect of omitting a meal on cognitive performance remains equivocal: from the outset, idiosyncrasy has prevailed. Yet, for young and nutritionally vulnerable children, breakfast is more likely to benefit than hinder performance. For nutrient composition, despite inconsistencies, some cautious predictions can be made. Acutely, carbohydrate-rich–protein-poor meals can be sedating and anxiolytic; by comparison, protein-rich meals may be arousing, improving reaction time but also increasing unfocused vigilance. Fat-rich meals can lead to a decline in alertness, especially where they differ from habitual fat intake. These acute effects may vary with time of day and nutritional status. Chronically, protein-rich diets have been associated with decreased positive and increased negative affect relative to carbohydrate-rich diets. Probable mechanisms include diet-induced changes in monoamine, especially serotoninergic neurotransmitter activity, and functioning of the hypothalamic pituitary adrenal axis. Effects are interpreted in the context of individual traits and susceptibility to challenging, even stressful, tests of performance. Preoccupation with dieting may impair cognition by interfering with working memory capacity, independently of nutritional status. The change in cognitive performance after administration of glucose, and other foods, may depend on the level of sympathetic activation, glucocorticoid secretion, and pancreatic β-cell function, rather than simple fuelling

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Abbreviations: CCK, cholecystokinin; IQ, intelligence quotient; LNAA, large neutral amino acids; MFF, Matching Familiar Figure; TRP, tryptophan; TYR, tyrosine; 5-HT, serotonin.
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of neural activity. Thus, outcomes can be predicted by vulnerability in coping with stressful challenges, interacting with nutritional history and neuroendocrine status. Functioning of such systems may be susceptible to dietary influences on neural membrane fluidity, and vitamin-dependent cerebrovascular health, with cognitive vulnerability increasing with age.

Glucose: Cognition: Cortisol: Memory: Stress

Introduction

The present review is concerned with interpreting the somewhat inconsistent findings from research into effects of food and nutrients on cognitive function. Can patterns be discerned that allow better prediction of responses to nutritional changes, based on knowledge of individual characteristics? Could research findings in this area be better understood as interactions between affective state and cognitive function? The view is taken that assessment of cognitive function involves challenging, even stressful, tasks, on which performance may both elicit and depend on changes in affective state and stress responses. This conceptualisation allows nutritional effects on cognitive function to be mediated by changes in affect or arousal as well as or instead of direct effects on perception, attention and memory. Furthermore, it is argued that more emphasis should be given to both inter- and intra-individual differences in nutritional, arousal and stress-coping status, since these may reflect variation in susceptibility of neurohormonal systems to nutritional manipulation.

Nutritional variation v. malnutrition

Chronic malnutrition undoubtedly hinders cognitive development and performance (Kretchmer *et al.* 1996; Dauncey & Bicknell, 1999). However, the present review is not concerned with that literature, nor with the pharmacological effects of ingested substances such as caffeine or alcohol (Rogers, 1995; Bellisle *et al.* 1998); instead, we review the evidence that acute variation in nutritional status, such as through omission of a meal or by eating a meal of particular composition, may influence cognitive performance or arousal. The impact of variation in nutritional indicators such as blood glucose or vitamins is also included, where these may be considered as measures of nutritional status among populations not overtly malnourished. The susceptibility of cognitive function to such variation may depend on other factors, such as age and vulnerability to stress.

Impact of meals on mental function and arousal

'…fits of drowsiness are especially apt to come on after meals' Aristotle (350 BC)
'On Sleep and Sleeplessness' (translated by J. I. Beare)

The postprandial period has long been associated with a restful, quiescent state (Hutchinson, 1952); indeed, in many cultures, a post-lunch nap or 'siesta' is built into the society's daily rhythm. Conversely, hunger has been associated with activation and arousal, poor attention, irritability and aggression (Carlson, 1916; Laessle *et al.* 1996; Kleinman *et al.* 1998).

So, are we more alert and mentally efficient, or over-aroused, distracted and less efficient, before eating than after? It is well established that sympathoadrenal arousal enhances memory formation (McGaugh, 1989). Yet, although eating might be considered to be the antithesis of a 'flight or fight' state of arousal, it has been recognised for some time that food ingestion causes an acute rise in sympathetic nervous system output, resulting, for instance, in an increase in cardiac activity (Young & Landsberg, 1977; Vaz *et al.* 1995; Biston *et al.* 1996). Thus, eating and arousal are not simple opposites. Indeed, eating a meal, or at least its post-ingestive consequence, is a substantial challenge to the body's homeostasis, and in that sense has been viewed as a stressor (Woods, 1991). However, whereas most stressors are potentially harmful, leading to stress responses designed to avoid or minimise their effects, ingestion and absorption of nutrients are, normally, of benefit, and often essential, to the organism. Nevertheless, the body needs to prepare and react appropriately to this sudden influx of nutrients, if their absorption and use are to be optimal, and minimally disruptive. As our eating habits become established, the brain and body become tuned for rapid and appropriate preparation, based on anticipation of meal composition and after-effects, through early detection of sensory and nutritional properties (Woods & Strubbe, 1994; Teff, 1996). It is within this context that acute nutritional influences on cognitive function and arousal need to be considered.

First, we address evidence for the importance of meal timing during the day, dealing with studies of overall meal effects, in the context of circadian rhythms. Then we consider the influences of the size and composition of meals, in particular where findings suggest mechanisms of susceptibility.

The importance of meal timing

In man, as in many other animals, there are circadian rhythms and sleep–wake cycles in arousal and performance, which complicate interpretation of the impact of meals. Why should a 'siesta' be needed after lunch, but not after breakfast or an evening meal? Whereas there are many examples of a decline in feelings of vigour and increases in sleepiness in the hours after a midday meal (Lieberman *et al.* 1986; Smith & Kendrick, 1992; Owens *et al.* 2000), it is often not clear whether this is due to eating a meal or merely the time of day. Folkard & Monk (1985) concluded that this 'post-lunch dip' in performance or arousal probably has both endogenous and exogenous components; when subjects were isolated from time cues, diurnal deterioration in performance similar to the post-lunch dip was seen, but independently of meal timing.

Self-reported alertness or energy rises to a peak in the late morning or midday, then falls later in the waking day (De Castro, 1987*a*; Smith, 1992). Circadian changes in alertness have often been linked to changes in core body temperature, considered a correlate of physiological arousal (Folkard & Monk, 1985; Owens *et al.* 2000). Yet, in rats at least, there are clear preprandial rises and postprandial falls in core temperature (Woods & Strubbe, 1994); such meal-dependent changes in body temperature do not appear to have been clearly dissociated from temperature-alertness correlations in human subjects (Christie & McBrearty, 1979). These circadian considerations are not trivial, as circadian rhythms of major hormonal systems such as the glucocorticoids have been shown to be entrainable by feeding regimens (Dallman *et al.* 1993).

By contrast to subjective alertness, however, circadian changes in cognitive performance have recently been dissociated from core body temperature (Owens *et al.* 2000). Perceptual-motor (e.g. reaction time) and other attention-based tasks seem to be performed faster but less accurately later in the day, possibly due to attention becoming less focused as time passes

(Smith, 1992). The circadian pattern of performance on tasks substantially involving memory depends on the level of memory load imposed, so that tasks with greater load are actually performed best earlier in the day (Folkard & Monk, 1985; Owens *et al.* 2000). This may in part reflect an inability of less demanding tasks to overcome sleep inertia (Owens *et al.* 2000), which can impair performance for 2–4 h after waking (Jewett *et al.* 1999). Another implication is that the timing of peak performance will depend on how demanding an individual participant finds the task.

Other circadian changes may also be important; for instance, test anxiety levels have been found to be higher in the afternoon (Smith, 1985), while spontaneous (anticipatory) anxiety may be higher in the morning (De Castro, 1987*b*). Furthermore, neurochemical and hormonal activity and function vary across the day, as well as in response to meals (Van Cauter *et al.* 1992; De Kloet *et al.* 1993), as does availability of energy substrates including glucose (Shapiro *et al.* 1991; Biston *et al.* 1996; Owens *et al.* 1996). Therefore, the effects of meals on performance and arousal could be expected to vary over a 24-h period. Thus, evidence for acute effects of meals on particular aspects of performance, for instance, may reflect the circadian context of those meals and tasks, as much as any nutritional impact.

Effects of breakfast in children. Interest in the influence of breakfast on subsequent mental and physical performance remains considerable, especially because of the concern that missing breakfast might impair learning in schoolchildren (Pollitt & Mathews, 1998). However, evidence in support of this belief is equivocal (Smith *et al.* 1994*b*). In an editorial review of the oft-cited Iowa breakfast studies of Tuttle and colleagues in the 1950s (Anonymous, 1957), it was concluded that '…there is a considerable degree of variation between individuals in their physiologic and, no doubt, emotional response to breakfast'. In later studies, some attempts have been made to take into account possible sources of such individual variation. For instance, early on there was some support for the idea that any change from a child's habitual eating patterns would lead to a worsening of performance, irrespective of what is or is not eaten (Richards, 1972). This issue gained further support in later studies of the impact of meal size and composition (see p. 177).

In an influential study of effects of omitting breakfast in thirty-four 9–11-year-old children, individual differences clearly affected the outcome (Pollitt *et al.* 1981). This study is considered in some detail here, because it was the first of this kind to address possible mechanisms by comparing levels of energy substrates with performance measures, and serves to illustrate some of the complexities of interpretation of results in this area. In this within-subjects design, omitting breakfast produced an increase in errors on four easier problems (fewer choices) in a task of visual discrimination (Matching Familiar Figure (MFF) test), but only in subjects whose intelligence quotient (IQ) was below the median. This suggested that higher-IQ children may have been insufficiently taxed by these problems to be affected by acute fasting. Combining both easy and hard problems, errors were increased in those children in whom omitting breakfast reduced blood glucose level, independently of IQ. Curiously, in the fasting condition only, higher-IQ children with above average absolute glucose levels took longer to respond on the hard items than such children with low glucose levels; response time in lower-IQ children was shorter than for higher-IQ children, and was independent of absolute glucose levels. Errors on the hard items did not differ by IQ or glucose in this analysis. This finding suggests that whatever process is maintaining blood glucose during fasting (see p. 186), the higher the blood glucose level achieved, the less efficient are the higher-IQ children in this MFF task. We will return to this issue of glucoregulation and performance later, when discussing studies in adults that specifically sought to relate blood glucose to performance. However, one potential con-

founder that needs to be considered is time since awakening, as the earlier risers may have both lower blood glucose and less sleep inertia. Also, given the discussion earlier on circadian changes in peak performance and memory load, another point should be noted here: for an IQ-dependent memory task, lower-IQ children would be more likely to achieve their peak performance in the morning than would higher-IQ children.

In addition, omitting breakfast actually improved accuracy for the last item on a serial recall memory test (Hagen Central Incidental test), for all the children.

Whilst blood glucose level was not affected on average by missing breakfast, lactate, non-esterified fatty acids and β-hydroxybutyrate were all elevated when breakfast was omitted (Pollitt *et al*. 1981). This situation probably results from sympathoadrenal and glucocorticoid stimulation of lipolysis, proteolysis, gluconeogenesis and muscle glycogenolysis, so releasing energy substrates while protecting liver glycogen stores (McMahon *et al*. 1988). However, it should be noted that these measurements, including glucose, were taken immediately after the cognitive tests, and so do not simply reflect fasting status, but may also be a consequence of stress or arousal during fasting. Pollitt *et al*. (1981) suggested that the intensity of this physiological response to fasting would be inversely proportional to blood glucose level. However, it is not clear why this should be the case following stress; in fasted and stressed rats, blood glucose only rises when adrenaline is released, and this stress-induced hyperglycaemia is independent of glucocorticoid release (Yamada *et al*. 1993). If adrenaline release is prevented (by adrenomedullation), blood glucose falls in stressed fasted rats, whereas hyperglycaemia in stressed fed rats is not so dependent on adrenaline (Yamada *et al*. 1993). Indeed, it is clear that an important mechanism by which adrenaline enhances blood glucose is by inhibition of uptake and disposal of glucose (Sherwin & Saccà, 1984). Thus, we suggest that lower blood glucose during fasting and after stress may instead reflect a weaker adrenergic response.

If that is the case, then lower adrenergic arousal might contribute to the increased error rate on the MFF task in children whose blood glucose was lower when missing breakfast than with breakfast. During fasting, the increased latency to respond on this task would, on this argument, be associated with a greater adrenergic arousal, specifically in higher-IQ children. Perhaps such arousal interfered with decision making on this task in more thoughtful children, or reflected greater involvement or anxiety; final error rates were unaffected. The fasting-induced increased error rate, on easy MFF items, among lower-IQ children, might reflect an interaction between task engagement and fasting-induced arousal.

In an extension of this design on a further thirty-nine 9–11-year-olds, Pollitt *et al*. (1983) found more consistent results after statistically controlling for latency to respond (which was again longer in higher-IQ children, and so in part controls for IQ level, and perhaps demand and involvement too). This time, omitting breakfast resulted in significantly lower (post-test) group mean blood glucose, and lower insulin levels (not measured in the first study). Omitting breakfast increased the number of errors on the MFF test (adjusted for response time), irrespective of IQ level. For the hard problems only, children with lower post-test blood glucose and insulin produced more errors, which could reflect a lack of engagement.

Interestingly, omitting breakfast resulted in better recall of the incidental objects in the Hagen Central Incidental test, i.e. those to which the children were not instructed to attend, but which were paired with the target figures. Importantly, this score of attention to irrelevant stimuli is known to correlate positively with increased anxiety (Dusek *et al*. 1976). Furthermore, this incidental attention score was greater in children with lower post-stress insulin (but not glucose) levels during fasting. This would be compatible with suppression of insulin release by greater arousal or stress in more anxious children.

Further evidence that fasting due to omitting breakfast can have an arousing effect under

challenge was provided by a study comparing cardiac and cortical evoked potential orienting responses after breakfast or no breakfast in 9–11-year-old children (Conners & Blouin, 1983). Vigilance errors and performance variability increased over three morning test periods, but to a greater extent when fasting. Likewise, arithmetic was, increasingly over the morning, better with breakfast than without. Like performance, the breakfast–no-breakfast differences in the physiological data increased during the morning, suggesting that breakfast might aid performance by restraining sympathoadrenal reactivity, which was exaggerated when fasted.

When considering possible nutritional mechanisms, it is important to note that beneficial effects of breakfast on performance have been found 3 h after the meal (Pollitt & Mathews, 1998), when blood glucose is likely to have returned to pre-meal levels. Nevertheless, Pollitt *et al*. (1981) argued cogently that young children were likely to be more susceptible to effects of brief fasting than adolescents or adults, due to greater brain metabolic demands relative to liver and muscle glycogen and to gluconeogenic capacity. This argument seems largely to have been overlooked by later workers in this area, but may yet be worth bearing in mind; indeed, uncontrolled individual differences in glycogen stores at the time of participation might explain much of the variation. Pollitt & Mathews (1998) reviewed evidence suggesting that the beneficial effects of breakfast on mental performance may be greater for children with a history of malnutrition.

This increased nutritional sensitivity of performance in younger children might underlie data from a much larger sample of 595 schoolchildren ranging in age from 11 to 18 (Dickie & Bender, 1982). There was no consistent evidence for an influence of morning food intake, or its lack, on memory and attention, overall. However, among the younger children only (average age 12·5 years), the mean test scores indicated a tendency for slower speed and less accuracy in subjects omitting breakfast, although no statistical comparison of these group means was reported.

It can be seen that consistent evidence for a beneficial effect of breakfast on cognitive performance remains elusive. In particular, we suggest that individual differences in engagement and task demand will obscure any relationships between breakfast, or breakfast-dependent changes in blood glucose, and mental performance. There remains a need for more tightly controlled studies of the possible effects, and mechanisms of action, of breakfast in large samples of children.

Effects of breakfast in adults. Effects of breakfast, or its omission, on performance are not limited to children, despite the argument that children, especially if poorly nourished, might be most sensitive to short-term fasting. Even so, few studies in adults have simply compared effects of breakfast with its omission on performance. In thirty-three healthy university students, omitting breakfast lengthened the time taken to complete spatial and verbal recall tasks 2 h later, compared with a group consuming a protein-rich 'milk-shake' (1368 kJ (327 kcal); % energy as protein, carbohydrate, fat: 23, 43, 34, respectively) for breakfast (Benton & Sargent, 1992). Accuracy did not differ between these groups, so clearly the fasted group was performing less efficiently. Within this group, higher blood glucose predicted faster completion of the spatial memory task. Within the non-fasted group, higher blood glucose predicted fewer errors on this task. Although no measures of mood or arousal were reported, these findings may indicate differences in test-induced sympathoadrenal or adrenocortical arousal across subjects within a group, mediating both hyperglycaemia and increased speed of performance. However, interpretation is limited by uncertainty as to when the glucose was measured, and whether other glucose–performance correlations differed statistically from those mentioned. Furthermore, the milk-shake might have induced effects that would not be apparent after a habitual breakfast.

Two more recent studies in adults (Smith *et al*. 1994*b*; 1999*a*) addressed whether effects of breakfast were specific to memory-based tasks or included tasks assessing sustained attention,

reaction time, and logical or semantic reasoning. In both studies, mood and performance were measured at 1 and 2 h after breakfast; pre-breakfast measures were used as covariates.

In line with previous findings, Smith *et al*. (1994*b*) found (in students; 8–12/group, two studies) that breakfast improved free recall and recognition of words, whereas attention-based and reaction-time tasks were unaffected. Logical reasoning was slightly impaired 2 h after breakfast.

The later study (Smith *et al*. 1999*a*), inspired by more consistent effects of breakfast on memory tasks than on attention, investigated effects of breakfast specifically on different components of memory in students (thirty-six per group). The only effect of breakfast detected was an improvement in spatial memory. This is a replication of an earlier finding (Benton & Sargent, 1992); nevertheless, the lack of benefit of breakfast on a task requiring recall of a series of digits is surprising given that other studies found improvements in word list recall tasks (Benton & Sargent, 1992; Smith *et al*. 1994*b*). One possibly important difference between the later study and the previous two was that Smith *et al*. (1999*a*) did not provide a standard 'breakfast', but allowed students to choose how much cereal to eat.

Another problem with these studies is that it is difficult to dissociate completely effects of caffeine or its absence from those of breakfast or its omission. Even though Smith *et al*. (1994*b*, 1999*a*) included caffeine and no-caffeine groups, any effects of breakfast or its absence in the no-caffeine group may be confounded by caffeine withdrawal. Indeed, withdrawal would have been the situation at baseline for many subjects irrespective of group. It is also not clear what knowledge or expectations about the design were held by subjects; these could have been further sources of artefacts.

Neither of these studies found any effect of personality type, such as extraversion or neuroticism (see p. 175), although it is not clear whether the samples included sufficient variation in these traits to test such relationships effectively (unstable neurotics may be harder to recruit). Furthermore, such traits may become more influential later in the day (Smith, 1992).

Effects of the midday meal. As mentioned earlier, a quite consistent finding has been a drop in performance after the midday meal, known as the 'post-lunch dip' (Folkard & Monk, 1985; Smith & Kendrick, 1992; Owens *et al*. 2000). It appears that performance on tasks requiring sustained attention are more likely than briefer tasks of selective attention to be attenuated by lunch (Christie & McBrearty, 1979; Smith & Miles, 1986*b*). However, it remains unclear to what extent the 'post-lunch dip' actually depends on eating lunch (Folkard & Monk, 1985); an underlying rhythm in performance also seems likely to contribute, since vigilance was worse in the early afternoon than late morning, in subjects not eating lunch (Smith & Miles, 1986*a*).

An intriguing finding was that subjects' scores on the extraversion and neuroticism scales of the Eysenck Personality Inventory correlated, respectively, positively and negatively with the post-lunch dip in performance (Craig *et al*. 1981). Thus, stable extraverts were more vulnerable to post-lunch dip. This finding was replicated on a vigilance task by Smith & Miles (1986*a*), who in addition found that pre-lunch–post-lunch changes in state anxiety correlated (*r* 0·83) with pre-lunch–post-lunch differences in vigilance performance. That is, the greater the reduction in anxiety after lunch, the greater the drop in performance. So, it appears that anxious individuals, not calmed by lunch, maintain their level of performance after the meal. Similarly, when subjects were aroused by noise stress, no post-lunch dip in performance was seen, although pre-lunch performance was worse with noise (Smith & Miles, 1986*a*). An earlier finding may be of particular importance here: Christie & McBrearty (1979) found that stable extraverts showed a greater peak and subsequent decline in blood glucose after lunch than neurotic introverts. This greater change in blood glucose was also associated with less 'activated'

mood and slower cognitive performance. Possible implications of these findings are discussed later (p. 187), when we consider glucoregulation and cognitive performance in more detail.

Between-meal snacks. Kanarek & Swinney (1990) investigated whether an afternoon snack (1004 kJ (240 kcal) yoghurt or 1213 kJ (290 kcal) confectionery) would affect cognitive performance (15–60 min later) of male students, if eaten about 3 h after lunch or after no lunch. A zero energy 'diet' drink was used as a snack 'placebo' (subjects were blind to energy content). Both breakfast and lunch were standardised. Eating the energy-containing snack had a beneficial effect on memory, arithmetic reasoning, and reaction time on a continuous performance task. Reading speed was not affected by snack condition, although, in the second experiment, reading was slower if no lunch was given. The only other effect of lunch was that the snack-induced improvement in arithmetic reasoning in the first experiment did not occur without lunch. These results are impressive in their replicability and statistical significance in a small number of subjects (eighteen in all). However, they are hard to interpret mechanistically. If presence or absence of lunch had little or no impact on the snack effect, direct nutritional effects may not be important. Pre-absorptive psychological or physiological reactions to the sensory properties of the snacks may be involved (effects were seen on the first test 15–25 min after eating the snack) or the influence of expectations could be important. The timing of this snack intervention may be critical, but makes comparison with meal effects difficult. Although the snacks were perhaps eaten rather too late to influence any post-lunch dip (Craig, 1986; Smith & Kendrick, 1992), it was at a time of day when alertness, energy and memory performance are starting to decline (De Castro, 1987a; Smith, 1992). Moreover, these beneficial effects of afternoon snacks apparently do not occur in the late morning (unpublished data cited in Kanarek & Swinney, 1990). Perhaps, eating the snack provided sufficient arousing stimulation, irrespective of nutritional consequences, to enhance performance during normal circadian decline.

Effects of evening meals. There are very few data on the effects of evening meals on mood and performance, which probably reflects the greater inconvenience of conducting research later in the day. Even so, given circadian changes in numerous variables that might be implicated in such effects, including mood and performance, as well as physiological variables, it seems likely that differences between evening and earlier meals would occur. When changes in performance after a meal in the middle of a nightshift were compared with after lunch, some differences were found (Smith & Miles, 1986a); for instance, the midday meal impaired speed and accuracy, whereas only accuracy was impaired during the nightshift. Also, whereas anxious subjects showed resistance to lunch, anxiety level did not affect responses to the nightshift meal.

Smith *et al*. (1994c) studied the effects of a large evening meal (5·02–6·28 MJ (1200–1500 kcal)), freely chosen from a college refectory, on mood, performance, blood pressure and heart rate, in twenty-four men and twenty-four women. Half the subjects had no meal, and half had caffeine added to decaffeinated coffee. Measures were taken pre-meal and 90 and 180 min after starting eating. We will consider only the meal effects here. At 3 h after starting eating, pulse rate but not blood pressure was higher after the meal than after no meal. By this time, subjects who omitted the meal felt more feeble and incompetent, while these feelings did not change in fed subjects. Also, after eating, subjects felt more outward-going compared with fasted subjects. However, out of six performance tests, repeated twice, there was little evidence for consistent differences between fed and fasted subjects, which suggests that performance was not clearly related to changes in subjective mood.

Influence of meal size

It might at first seem obvious that a large meal would have a different impact from a small meal, but a number of difficulties arise in trying to establish evidence for such a difference. For example, how much bigger should the large meal be, or how small can the small meal be? Should the size comparison be in terms of energy, volume, weight, consumption time, or all of these? When should behavioural outcome measures be taken? For instance, 1 h after eating, the amount of nutrients absorbed from a small meal may not differ appreciably from that absorbed after a large meal, though the volume of food remaining in the stomach will of course differ. Does the meal differ in size from each subject's habitual meal, and is that important? What form of 'dose–response' pattern would be expected? Does meal size interact with time of day?

Few of these issues have been addressed systematically, as the majority of studies in this area have used meal sizes that were standardised and more or less resembled typical breakfasts or lunches for the subjects concerned, or subjects were allowed to self-select their own meals. Nevertheless, there are some exceptions; for instance, Craig & Richardson (cited in Craig, 1986) compared the effects of a heavy (about 4·18 MJ (1000 kcal)) and a light (<1·26 MJ (300 kcal)) meal on performance on a letter cancellation task (no further meal details were given). On average relative to pre-lunch performance, more letters were missed after the heavy meal, whereas fewer letters were missed after the light lunch. However, these effects were not apparent in those subjects for whom the experimental meal was of similar size to their habitual lunch.

When the energy content of lunch was varied in increments of 40 % (the middle-sized meal equivalent to one third of energy requirements), only the largest meal affected cognitive performance, with more errors occurring on tests of attention and vigilance 1 h later (Smith *et al.* 1991). Meal size did not affect mood, but positive affect (e.g. alertness, interest) declined equally after all meals. In that study, proportions of macronutrients had been kept constant (and typical), but when a lunch with 50 % more energy contained additional fat, performance on such tasks tended to be slower but more accurate (Smith *et al.* 1994*a*). Subjects also felt calmer after the high-fat meal. However, those small effects on performance and mood interacted with meal weight, which was independent of fat content in that design.

Two studies have compared large and small breakfasts on performance and mood. In adolescents, a larger breakfast (on average 2653 ± 996 kJ (634 ± 238 kcal) *v.* 1628 ± 791 kJ (389 ± 189 kcal)) resulted in poorer vigilance but better short-term memory, 3 h later (Michaud *et al.* 1991), although there was no evidence of an energy dose–response effect (when intake was grouped by 418 kJ (100 kcal) steps). Alertness and tranquillity, and post-test blood glucose, were unaffected by size of breakfast. In 10-year-old children, a larger breakfast improved verbal fluency, at least in boys (2243 kJ (536 kcal) *v.* 711 kJ (170 kcal) on average), whereas eating very little for breakfast was associated with comparatively worse mood and performance on simple tasks (Wyon *et al.* 1997). However, the design did not exclude the possibility that underlying motivation could have contributed to both breakfast consumption and task performance.

In an observational study in a residential laboratory, in which energy content of breakfasts and lunches varied, there was little evidence of any relationship between meal size and performance measures (mood was not reported) (Kelly *et al.* 1994). However, effects may have been obscured by lack of control of nicotine and caffeine consumption in the small number of subjects.

Overall, it appears that meal size can influence performance, but for better or worse depending on the nature of the task. Also, there is likely to be a trade-off between sufficient energy supply and demands on processes of absorption and metabolism and associated neurohormonal systems. Mood does not appear to be particularly sensitive to meal size, unless very

little is eaten or stress is present; when subjects were stressed by noise, higher energy intake prevented deterioration of mood (Macht, 1996). However, it is difficult to compare the few studies in this area, and, as we shall see, within reasonable limits, composition may be more influential than absolute size.

Meal composition, performance and mood

Protein v. carbohydrate

There has been rather more research interest in the effects of meal composition, especially macronutrients, on mood than on cognitive performance (Rogers, 1995). This is largely because of evidence that plasma and brain levels of precursor amino acids for synthesis of monoamine neurotransmitters, strongly implicated in affective disorders, can depend on carbohydrate : protein ratios in the diet (Wurtman *et al*. 1981). Synthesis of serotonin (5-hydroxytryptamine; 5-HT) depends on dietary availability of the precursor essential amino acid, tryptophan (TRP), due to a lack of saturation of the rate-limiting enzyme, tryptophan hydroxylase (Fernstrom, 1983). An important complication is that TRP competes with several other amino acids, the large neutral primarily branched-chain amino acids (LNAA), for the same transport system from blood to brain. If the protein content of a meal is sufficiently low, such as 5 % (or less) total energy as protein, then relatively few amino acids will be absorbed from the food in the gut. At the same time, insulin will stimulate tissue uptake of competing amino acids from the circulation, and the plasma ratio of TRP to those amino acids (TRP : LNAA) will rise, favouring more TRP entry to the brain (Fernstrom, 1983; Yokogoshi & Wurtman, 1986). Conversely, a high-protein meal, which would be less insulinogenic, results in absorption of large amounts of competing amino acids into the blood, especially the branched-chain amino acids, leucine, isoleucine and valine. On the other hand, TRP is scarce in most protein sources, and is readily metabolised on passage through the liver; thus, the plasma ratio of TRP to competing amino acids falls after a protein-rich meal (Schweiger *et al*. 1986*b*; Yokogoshi & Wurtman, 1986; Christensen, 1993). Indeed, the protein-induced reduction in plasma TRP ratio often seems to be more marked than any carbohydrate-induced rise (Lieberman *et al*. 1986; Lyons & Truswell, 1988; Wolever *et al*. 1988; Christensen & Redig, 1993). Such effects also depend on the interval since, and nutrient content of, the last meal (Fernstrom & Fernstrom, 1995).

This evidence is particularly relevant to dietary effects on mood and arousal, because 5-HT has long been implicated in sleep, as well as affective disorders such as depression and anxiety (Huether, 1988; Cowen, 1996). However, cognitive performance might also be affected, given the known role of 5-HT in responsiveness to environmental stimuli and stressors, impulsivity and information processing (Spoont, 1992; Cowen, 1996). Importantly, there is evidence that dietary availability of TRP can influence brain function in humans; for instance, feeding a TRP-free diet, which considerably reduced plasma TRP (and so presumably impaired 5-HT function; Stancampiano *et al*. 1997), induced depression in previously recovered depressives or in people with a genetic predisposition to depression (Benkelfat *et al*. 1994; Heninger *et al*. 1996). Furthermore, a TRP-free drink has been shown to impair performance on tests of visuospatial and visual discrimination learning (Park *et al*. 1994) as well as consolidation of long-term memory (Riedel *et al*. 1999). This latter memory impairment was found not to depend on mood changes or history of depression (Riedel *et al*. 1999).

There have been several recent reviews of this area (Bellisle *et al*. 1998; Reid & Hammersley, 1999; Dye *et al*. 2000), so the earlier work will only be summarised briefly here. Spring *et al*. (1983) compared effects of protein-rich (86 % energy as protein, trace carbohy-

drate) and carbohydrate-rich (80 % carbohydrate, protein-free) snacks (about 1088 kJ (260 kcal)) on mood and performance 2 h later. Results were variable, depending on age, gender and time of snack. However, there was a tendency for more sleepiness and calmness after the carbohydrate snack than after the protein-rich one. In subjects aged at least forty, lapses in sustained attention followed the carbohydrate lunch.

The increased sleepiness and calmness is compatible with an increase in 5-HT function, mediated by increased brain uptake of TRP, after the carbohydrate-rich, protein-free meal. Increased fatigue, and decreased alertness, have also been reported after oral TRP (50 mg/kg; Lieberman *et al*. 1983). However, that study did not show any effect of TRP on performance, so differential effects of carbohydrate and protein on performance may not simply reflect changes in TRP availability (although oral dosing with TRP is not equivalent to dietary manipulation of plasma TRP).

Furthermore, sleepiness (a common postprandial state) may have been inhibited after the protein-rich meal by a reduction in the ratio of TRP to other amino acids competing for uptake into the brain (Lieberman *et al*. 1986; Wolever *et al*. 1988), so reducing 5-HT synthesis. Comparing effects of carbohydrate to protein (Wolever *et al*. 1988; Christensen & Redig, 1993) does not dissociate these two possibilities. Moreover, in a similar study comparing carbohydrate- and protein-rich meals on mood and performance, Lieberman *et al*. (1986) did not find differential effects of these macronutrients on fatigue or alertness, except for a transiently slower reaction time after the carbohydrate-rich *v*. the protein-rich lunch.

Another difficulty in comparing effects of carbohydrate and protein intake is that relative changes in mood and performance might be due to protein-induced raised plasma tyrosine (TYR) (Fernstrom & Fernstrom, 1994; Markus *et al*. 1998), the precursor amino acid for synthesis of catecholamines (adrenaline, noradrenaline, dopamine), which also competes with LNAA for entry into the brain. In catecholamine systems where the neurones are firing rapidly, acute physiological increases in brain TYR, e.g. by feeding a high-protein diet, can raise TYR hydroxylation rate and catecholamine turnover (Fernstrom & Fernstrom, 1994). Such systems include dopaminergic neurones involved in arousal, attention and motivation. Nevertheless, high-protein meals in human beings do not always raise the plasma TYR : LNAA, perhaps depending on nutritional status or time of day; a protein-rich meal after overnight fasting led to a fall in TYR : LNAA in healthy females, while in underweight anorectic women, the ratio rose, due to a marked postprandial increase in plasma TYR (Schweiger *et al*. 1986*b*). Also, unlike TRP, a large oral dose of TYR did not affect mood or performance (Lieberman *et al*. 1983).

By contrast to the above effects of almost pure carbohydrate or protein meals, a lunch of 55 % energy as protein and 15 % as carbohydrate altered attention, producing faster responses to peripheral stimuli, but greater susceptibility to distraction, with no differences in mood, compared with eating the reverse proportions of protein and carbohydrate (Smith *et al*. 1988). However, these meals would not be predicted to alter brain levels of either TRP or TYR (Yokogoshi & Wurtman, 1986; Teff *et al*. 1989; Fernstrom & Fernstrom, 1995), which could explain why post-lunch increases in lethargy and sleepiness were not affected by macronutrient composition in that study.

Evidence for an interesting synthesis of ideas concerning dietary manipulation of 5-HT function, performance and mood has been provided recently by Markus *et al*. (1998, 1999, 2000*a*). They hypothesised that raising brain TRP by eating a carbohydrate-rich–very-low-protein diet might protect stress-prone subjects from the mood-lowering and performance-reducing effects of an uncontrollable stressor. During stress, which is known to increase central 5-HT release (Wright *et al*. 1992), Markus *et al*. (1998) inferred that people with poor stress-coping ability might be susceptible to a functional deficit in 5-HT synthesis, which a dietary

increase in TRP supply might alleviate. Thus, subjects were classified as high or low on a neuroticism scale ('stress proneness'), and then on one day given a high-carbohydrate–protein-poor breakfast, snack and lunch, followed by a challenging arithmetic test and a letter-recognition (memory scanning) task. On another day, subjects received protein-rich–low-carbohydrate meals, followed by the same stress induction and task. There was indeed some evidence to support the hypothesised interaction between stress proneness (neuroticism) and diet. Ratings of depression and vigour increased and decreased respectively after stress, except in the single condition where neurotic subjects had eaten the high-carbohydrate–protein-poor diet (which clearly elevated plasma TRP : LNAA). In this case, no change in depression or vigour occurred. Furthermore, this was the only situation in which cortisol did not increase after stress (Markus *et al.* 1998). In contrast to mood, performance on the memory task did not interact with diet and personality. However, reaction times were faster for all subjects after the protein-rich diet. These dietary effects on depression and cortisol in stress-prone subjects were essentially replicated by Markus *et al.* (2000*b*).

In another report using a similar design, Markus *et al.* (1999) did find an interaction between diet and personality on performance; in stress-prone subjects only, the carbohydrate-rich–protein-poor diet improved reaction time and reduced errors on more demanding letter-recognition tasks, compared with the protein-rich–carbohydrate-poor diet. The key difference between the design of Markus *et al.* (1998) and this study was that now the stress task allowed subjects to solve the arithmetic more easily (though heart rate and skin conductance did not differ from less controllable stress). It is not clear why such effects on performance should interact with stress controllability in this way, although a complex balance between catecholaminergic and serotoninergic activity might be involved, since both TRP and TYR availability are affected by these diets (Markus *et al.* 1998). Even though Markus *et al.* (2000*a*) replicated the diet–neuroticism interaction effects on stress-induced depression and cortisol using high- and low-TRP protein diets (α-lactalbumin and casein, respectively), changes in TYR availability cannot be ruled out.

These results are particularly interesting in the light of a recent study of another response to protein-rich and protein-poor lunches (Gibson *et al.* 1999). The former but not the latter composition stimulated release of cortisol (Fig. 1). The protein-rich meal also prevented the post-lunch decline in positive affect (Fig. 2). Although there was no clear correlation between meal-induced cortisol release and post-meal mood changes (in only nine women), greater protein-stimulated cortisol secretion was associated with poorer overall psychological wellbeing (General Health Questionnaire). It has also recently been shown that an increase in positive affect 2–3 h after a protein-rich lunch is associated with a greater cortisol response to that meal, but only in subjects who ate a low-protein diet for 5 d previously (Gibson *et al.* 2000). These findings suggest a complex interaction between psychological wellbeing, nutritional status and corticosteroid reactivity. This hormonal response provides a possible alternative mechanism for differences in mood, and perhaps performance, after high-carbohydrate–protein-poor and low-carbohydrate–protein-rich meals described earlier. To avoid repetition, more detailed evidence for a role for cortisol in effects on performance and mood is discussed later (p. 189), in the context of effects of glucose on mental performance.

Effects of fat

Recently, investigators have moved away from comparing protein and carbohydrate, to address the possible role of varying fat intake on mood and performance. Typically, fat and carbo-
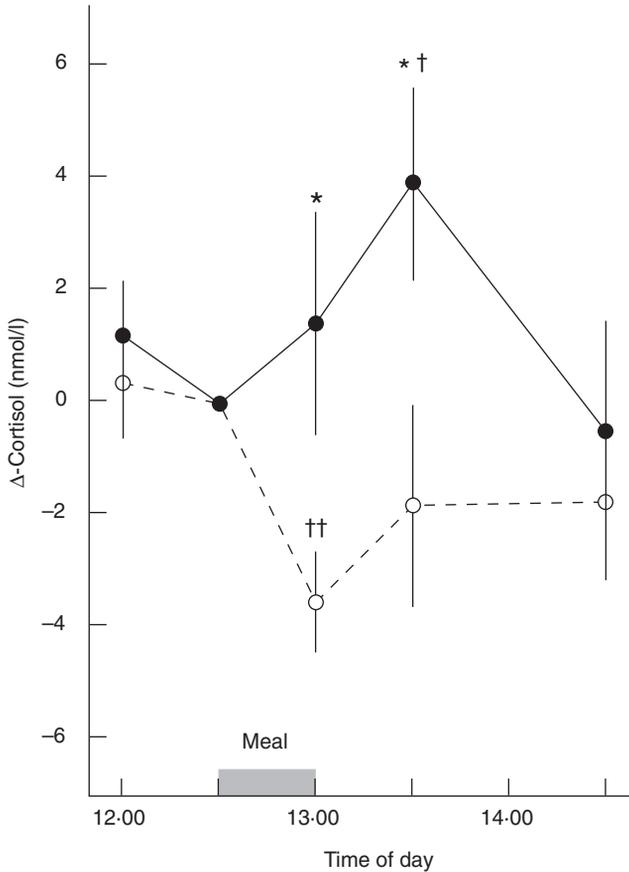
Fig. 1. Changes in salivary cortisol levels in women after eating a high-protein meal (——, 32 % energy as protein) and an equi-energetic low-protein meal (----, 5 % protein). Data are mean values for nine women with their standard errors represented by vertical bars. *Significant difference between meal conditions at that time ($P < 0.025$). Significantly different from baseline: †$P < 0.05$, ††$P < 0.01$. Data from Gibson *et al.* (1999).

hydrate levels were varied, with protein kept constant. Comparisons have been made for low-fat (e.g. 11–29 % of energy as fat), medium-fat (e.g. 45 %) and high-fat (e.g. 56–74 %) break-fasts, mid-morning and midday meals (Lloyd *et al.* 1994, 1996; Wells & Read, 1996; Wells *et al.* 1997) as well as intraduodenal infusions of lipid or saline (Wells *et al.* 1995). Again these studies have recently been reviewed (Bellisle *et al.* 1998; Dye *et al.* 2000), so we concentrate on discussing patterns in findings, and their possible mechanisms.

On balance, high-fat meals appear likely to increase subsequent fatigue and reduce reported alertness, but with little effect on cognitive performance, relative to high-carbohydrate–low-fat meals. However, there were inconsistencies relating to changes in specific moods and effects of meal timing. For instance, Lloyd *et al.* (1994) found that feelings of drowsiness, confusion and uncertainty increased after low- and high-fat lunches but not after a medium-fat lunch. There was also a post-lunch improvement in reaction time after the medium-fat but not low- or high-fat lunches; other performance measures were unaffected. In a similar study but with breakfasts, scores on a 'fatigue–dysphoria' mood factor were reduced after a low-fat–high-
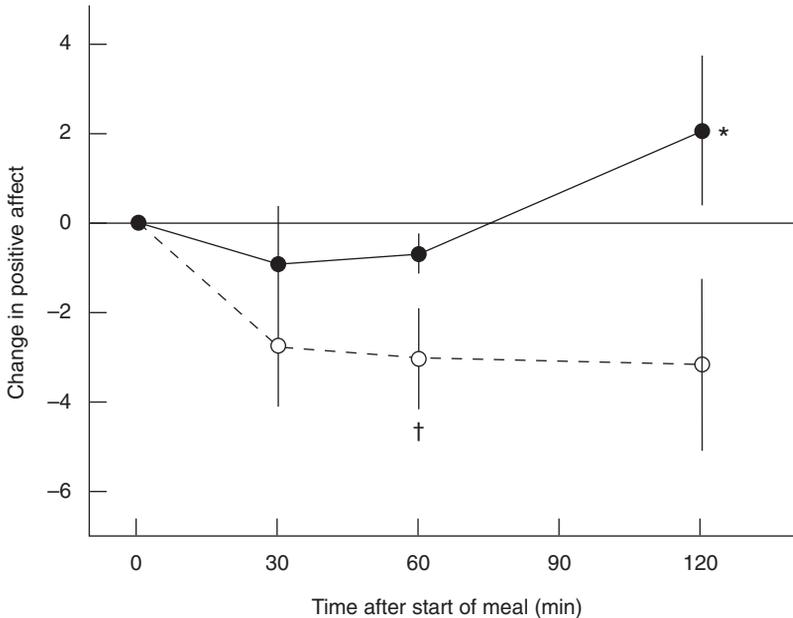
Fig. 2. Change in positive affect (differences from pre-meal baseline scores on the Positive and Negative Affect Schedule) in women after eating a high-protein meal (——, 32 % energy as protein) and an equi-energetic low-protein meal (----, 5 % protein). Data are mean values for nine women with their standard errors represented by vertical bars. *Significant difference between meal conditions ($P < 0.05$). †Significantly different from baseline ($P < 0.05$). Data are from Gibson *et al.* (1999).

carbohydrate breakfast (Lloyd *et al.* 1996). Given that these subjects' habitual lunch was probably medium-fat and their typical breakfast closer to the low-fat–high-carbohydrate version, it seems plausible that mood may be adversely affected by meals that differ substantially in macronutrient composition from habitual ones (Rogers & Lloyd, 1994; Dye *et al.* 2000), rather than by high- or low-fat *per se*. Another possibility is that similar mood effects could be induced (albeit by different mechanisms) by high-carbohydrate in one meal, and high-fat in the other; Cunliffe *et al.* (1997) found that 1674 kJ (400 kcal) drinks of pure fat or carbohydrate taken in the morning both increased an objective measure of fatigue (flicker fusion frequency) relative to a mixed-macronutrient drink, although the two single-nutrient drinks had opposite effects on plasma TRP : LNAA.

In the studies by Lloyd *et al.* (1994, 1996), mood differences were detected as early as 30 min after the meal, and so are unlikely to be due to changes in systemic nutritional state. Moreover, the meals were designed to disguise variation in fat level from the subjects. It is therefore possible that effects on mood may have resulted from discrepancies between subjects' expectations of certain post-ingestive effects, and the actual effects that resulted from neurohormonal responses to detection of specific nutrients in the duodenum and liver (Wells *et al.* 1995, 1998). A case in point may be the increase in tension, 90 min post-lunch, with increasing fat intake, reported by the predominately female subjects of Lloyd *et al.* (1994); we suggest that this finding might reflect an aversive reaction to (unexpected) fat-related post-ingestive sensations.

There is further evidence that any increase in fatigue directly related to fat is not likely to occur until the arrival of substantial amounts of fat into the duodenum 2–3 h later. Half an hour after low- or high-fat meals, alertness increased and sleepiness declined, whereas 2·5–3 h later fatigue increased while arousal declined to the greatest extent after a high-fat meal (Wells *et al.*

1995, 1997; Wells & Read, 1996). By comparison, when lipid was infused directly into the duodenum, a decline in alertness was apparent much earlier, by 30–90 min after the meal (Wells *et al.* 1995). Wells & Read (1996) found an increase in fatigue and reduction in vigour after a high-fat meal when eaten mid-morning but not at lunchtime (when mood changes were similar but independent of fat level). This could reflect either circadian effects or changes from habitual eating patterns. Nevertheless, on a sustained attention task, both speed and accuracy declined more rapidly after lipid infusion compared with saline, and after a high-fat *v.* low-fat midday meal (Wells *et al.* 1995).

A recent finding contrasts with the general trend for negative effects of fat ingestion: Fischer *et al.* (2001) fed subjects in the morning with equi-energetic (1674 kJ (400 kcal)) pure fat, protein or carbohydrate, in the form of sweet vanilla creams, designed to minimise differences in sensory acceptance between the foods. For the most part, a number of measures of cognitive performance (memory, attention and choice reaction time) improved after fat ingestion relative to those after protein or carbohydrate intake, with notably few effects on subjective ratings. This 'beneficial' effect of fat on postprandial performance was attributed to the demonstrated relative absence of glycaemic and hormonal (insulin, glucagon and cortisol) perturbations in the 3 h following fat ingestion. The limited effect of these pure nutrient meals on subjective measures might reflect suppression of expectations by the novel, disguised form of the foods. Even so, there was evidence for an arousing effect of protein relative to carbohydrate, in line with earlier findings.

How else might the proportion of fat ingested alter mood or mental performance? One possibility is via action of gastrointestinal and metabolic hormones. For instance, secretion of the gastric regulatory hormone, cholecystokinin (CCK), is particularly sensitive to increases in duodenal non-esterified fatty acids from breakdown of dietary fat (Schwizer *et al.* 1997); moreover, exogenous CCK can reduce arousal as well as appetitive responses to meal preparation (Stacher, 1985).

Wells *et al.* (1997) found that plasma levels of CCK and somatostatin increased to a greater extent after a high-fat, low-carbohydrate (74 %, 19 %, respectively) than after a low-fat, high-carbohydrate (11 %, 81 %,) equi-energetic meal, whereas the reverse was true for insulin and glucose (protein level was constant, if low, at 7 % of energy). Gastrin increased substantially but equally after both meals. Oxytocin showed a small increase after the high-fat meal, but no consistent increase after the low-fat meal. Possible associations between levels of hormones and mood were examined by stepwise multiple regression analysis on (log-transformed) absolute hormonal levels. Levels of fatigue were positively related to levels of CCK but negatively to gastrin levels. Sleepiness was positively related to insulin, but negatively to gastrin. However, no interactions with meal type were reported in these regression analyses, and indeed, changes in gastrin were unrelated to meal type in any case. Wells *et al.* (1997) suggested that the negative correlations between gastrin and fatigue–sleepiness may reflect less fatigue–sleepiness in more anxious subjects throughout the study, since trait anxiety has been associated with higher gastrin levels (Uvnas-Moberg *et al.* 1993). Certainly, without differential effects of meal type, it seems likely that personality will be an important mediating variable. It is thus not clear, though still a possibility, that differential effects of meal composition on hormones such as CCK underlie meal-specific changes in mood.

Effects of chronic dietary manipulations on mood and performance

There have been few studies of changes in mood and performance after chronic changes of dietary composition, as opposed to total intake. Two studies found increased negative affect and

anger after 1–3-week dietary regimens that differed substantially in macronutrient composition from subjects' usual diets (Deijen *et al*. 1989; Keith *et al*. 1991). However, it was not clear that this was due to specific nutritional effects, rather than a reaction to having to eat an unpalatable or monotonous diet.

Despite these methodological caveats, two other studies have linked greater positive affect and less negative affect with chronic (9 d or 6 weeks) relatively high-carbohydrate and low-protein intake (Schweiger *et al*. 1986*a*; De Castro, 1987*b*), although performance was not measured. Furthermore, Schweiger *et al*. (1986*a*) found that better mood was associated with higher average 24-h plasma TRP : LNAA. Nevertheless, more chronic studies of this type are needed before definitive conclusions can be drawn: for instance, both mood and TRP : LNAA could be raised by poor compliance with the required energy restriction. Also, in a recent study in which rhesus monkeys were fed diets differing in protein content for sequential 4-week periods, TRP and the 5-HT metabolite, 5-hydroxyindoleacetic acid, in cerebrospinal fluid were higher when higher protein levels were consumed (Grimes *et al*. 2000). This suggests that chronic protein-rich diets might raise brain 5-HT turnover, which is against the established evidence, primarily in rodents, for acute meal effects where protein-rich meals lower brain TRP (Fernstrom & Fernstrom, 1995). However, Grimes *et al*. (2000) found no association between these changes and plasma TRP : LNAA.

In fact, another mechanism is suggested by the finding that men eating a low-carbohydrate–protein-rich diet for 10 d had raised mean daytime plasma cortisol levels, compared with levels after eating a high-carbohydrate–low-protein diet (Anderson *et al*. 1987). No mood measures were reported in that study, but chronically high cortisol has frequently been linked to dysphoric mood and clinical depression (Checkley, 1996), although this might relate to dysfunction of brain 5-HT systems as well as the hypothalamic pituitary adrenal axis (Van Praag, 1996). Indeed, high baseline plasma cortisol predicts induction of depression by acute dietary TRP depletion (Åberg-Wistedt *et al*. 1998). By comparison with acute effects, any understanding of mechanisms underlying chronic effects will need to include neurotransmitter and neurohormone receptor adaptation (Huether *et al*. 1998).

Associations between changes in performance and mood after meals

Among those studies that have measured both mood and performance, there was some evidence that increased drowsiness or reduced arousal after meals was associated with deterioration in performance on vigilance or reaction time tasks (Smith & Miles, 1986*a*; Lloyd *et al*. 1994; Wells *et al*. 1995). However, other studies have found impaired performance with increasing arousal (Conners & Blouin, 1983), reduced arousal but no effect on performance (Lieberman *et al*. 1983), better mood but no effect on performance for fed *v*. fasted subjects (Smith *et al*. 1994*c*), or changes in performance but not mood (Smith *et al*. 1988; Fischer *et al*. 2001). This is perhaps not too surprising; causal relationships between mood and performance may well be neither contemporaneous (Owens *et al*. 2000) nor linear: for instance, optimal attention or memory may require some, but not too much, arousal, alertness and anxiety (McGaugh, 1989; Smith, 1992; Reid & Hammersley, 1999). It is also possible that subtle changes in mood are less easily detected than effects on performance; mood rating scales typically have poorer resolution and higher measurement error than most measures of cognitive performance. Furthermore, effects on mood may be much more idiosyncratic than those on performance; in a laboratory test situation, two participants may be equally aroused, yet one could interpret the situation negatively, the other positively (Reid & Hammersley, 1999).

In summarising the influence of meals on arousal and performance, it is clear that substantial inconsistencies abound. However, it is likely that, in the presence of stressful or demanding situations, certain vulnerable individuals will be susceptible to behavioural effects of their recent diet (Huether *et al*. 1998). The consequence could be a change in cognitive function, mood or both. In the following sections, we explore ways in which the outcome can depend on psychological, physiological and nutritional vulnerabilities.

Glucose and cognition

There is a body of evidence suggesting that manipulations of blood glucose levels result in alterations in cognitive processing efficiency. This evidence takes two forms, the first consists of studies indicating that raising plasma glucose levels by means of a glucose-laden drink or food results in improvements in task performance. The second strand of evidence comprises studies indicating that the lowering of glucose levels, or at least mobilisation of alternative energy stores, by means of food deprivation, is associated with declines in cognitive function. This work is based on the assumption that, since glucose is the major source of fuel for the brain (for example, see Sieber & Traystman, 1992), alterations in plasma levels of glucose will result in alterations in brain levels of glucose, and thus neuronal function. However, the strength of this notion lies in its common-sense plausibility, not in scientific evidence, and so the effects may well be epiphenomenal. For instance, blood glucose rises after all meals, when a plethora of neurohormonal responses are activated for glycaemic homeostasis (Widmaier, 1991). The roots of the glucose–cognition pairing can be found in the development of understanding, in the early 20th century, of adrenergic symptoms and cognitive confusion that follow diabetic hypoglycaemia. From this knowledge emerged the concept of reactive hypoglycaemia, in which non-diabetic patients complained of postprandial 'hypoglycaemic' symptoms, despite no apparent organic cause. Unfortunately, diagnoses far exceeded the evidence (Hutchinson, 1952; Service, 1999), leading to the emergence of a modern myth, influencing even research and health professionals (Lapp, 1981; Marks & Teale, 1993). These groups can still be heard misguidedly advising diabetic and non-diabetic patients to avoid 'simple' carbohydrates (now an obsolete term) for fear of inducing glycaemic highs then lows, despite years of evidence that many foods high in polymeric starches, such as bread and potatoes, have the highest glycaemic indices (Foster-Powell & Brand Miller, 1995; Food and Agriculture Organization/World Health Organization, 1998).

In relation to blood glucose and brain function, it should be noted that, in otherwise healthy individuals, the phrase 'hypoglycaemic symptoms' is misleading, in that the symptoms are not related to low blood glucose *per se* (Palardy *et al*. 1989; Snorgaard & Binder, 1990). Rather, there is evidence that some individuals reporting 'hypoglycaemic symptoms' have higher glycaemic thresholds for counter-regulatory hormone release (Snorgaard *et al*. 1991), and greater β-adrenergic sensitivity and insulin resistance (Berlin *et al*. 1994) during falling blood glucose, than non-symptomatic controls. Moreover, during insulin-induced hypoglycaemia, deterioration of visual reaction time occurred at higher blood glucose levels in 'hypoglycaemics' than in controls (Snorgaard *et al*. 1991), and in a number of subjects there was no detectable effect of hypoglycaemia on cognitive function in more complex tasks. However, a sensitive psychophysiological measure of cortical function (P300 wave latency) did suggest impaired brain function when insulin-induced hypoglycaemia became sufficiently low (falling from 4·8 to 4·0 mmol/l arteriovenous plasma glucose) to elicit counter-regulatory hormone release, despite absence of adrenergic symptoms (De Feo *et al*. 1988). It is also notable that psychiatric disturbances such

as anxiety and depression are commonly associated with self-reported hypoglycaemic symptoms (Berlin *et al*. 1994; Service, 1999).

The body of evidence concerning food deprivation, glucose and cognition is small and somewhat inconsistent in nature and relies on a combination of practice, the nature of the task battery employed and the exact meal that has been missed. For instance, as reviewed see p. 171, it has been found in several studies that missing breakfast impairs performance on measures of problem solving, decision time, and recall efficiency (Pollitt *et al*. 1981, 1983, 1996; Benton & Sargent, 1992). Conversely, such brief periods of fasting are also associated with improved performance on recognition memory tasks (Pollitt *et al*. 1981; Green *et al*. 1997*a*). Moreover, those studies provided no consistent evidence that performance deficits were due to deprivation-induced falls in blood glucose. At best, there was some association between better performance and higher blood glucose, typically measured after testing, but this was not shown to be simply a consequence of having recently eaten. Instead, it is likely to reflect individual differences in neurohormonal influences on glucose synthesis and uptake, interacting with task involvement and stress reactions, as well as nutritional state; for instance, stressful tasks delay gastrointestinal transit and peak glucose in some but not all subjects (Wing *et al*. 1990; Blair *et al*. 1991). Further, it has been found that periods of fasting ranging from the missing of a single meal to complete food deprivation for 24 h need not produce any significant changes in cognitive processing efficiency at all (Green *et al*. 1995).

The evidence relating to improvements in task performance resulting from the ingestion of a glucose load is more consistent in nature, although its interpretation remains unclear. Several studies have shown that the ingestion of a glucose drink improves performance on a number of measures of cognitive function, relative to the ingestion of a placebo drink or no drink at all; but methodological factors complicate interpretation of these studies. For instance, compared with fasted subjects, Lapp (1981) reported greater recall of nouns by hyperglycaemic subjects previously administered a 150 g glucose load 1 h after a 300 g carbohydrate meal. However, any subjects with intermediate plasma glucose levels, after either fasting or the glucose load, were excluded. This selection procedure is likely to group subjects by variation in physiological processes maintaining blood glucose, rather than by effects of carbohydrate loading *per se*. Furthermore, although the concentration of the glucose drink was not given, it was very likely to have been hypertonic, leading to gastrointestinal discomfort (Shuford, 1959). The amount of carbohydrate ingested was vastly in excess of a standard oral glucose tolerance test (50–75 g glucose in 200–300 ml), which itself is hypertonic and known to induce nausea (Phillips *et al*. 1996). Therefore, it is possible that autonomic activation or other consequences of gastrointestinal malaise contributed to differences in performance. In later studies, both the concentration and form of glucose (e.g. monohydrate, oligomeric) were rarely given, though doses and concentrations tended to be smaller (25–50 g in 200–500 ml), so it is not always possible to assess the degree to which hypertonicity may have confounded results.

Benton *et al*. (1987) found that administration of a glucose drink (25 g glucose, equivalent to a large banana) to children, 1·5–2 h after lunch, improved reaction time, relative to the administration of a saccharin-sweetened placebo drink. This type of finding has been replicated several times, using a number of different performance measures (for example, see Benton, 1990; Benton & Owens, 1993; Manning *et al*. 1993; Benton *et al*. 1994; Foster *et al*. 1998; for reviews, see Rogers & Lloyd, 1994). In general, the pattern of results from these studies suggests that glucose administration selectively improves short-term memory or improves performance on vigilance tasks that require a large component of 'working memory' for their successful completion. However, several complications are worth noting: first, time since, and nature of, the previous meal was often not controlled (Benton & Owens, 1993) and may have

contributed to variable results (Sundell *et al*. 1989; Martin & Benton, 1999); second, improved performance often did not depend on consuming a glucose load, but rather on the change in blood glucose over the test period, with or without a preload (Benton & Owens, 1993; Benton *et al*. 1994); third, some studies found no association between glucose ingestion and cognitive function (Azari, 1991), or negative associations between memory performance and increased blood glucose (Manning *et al*. 1990); fourth, others have found that improvements in performance can be associated with both rising and falling blood glucose (Benton *et al*. 1994; Craft *et al*. 1994; Parker & Benton, 1995; Donohoe & Benton, 1999*a*), or that a beneficial effect of glucose depends on efficient glucose uptake and disposal (Hall *et al*. 1989; Manning *et al*. 1990; Craft *et al*. 1994); finally, Green *et al*. (2001) have recently shown that enhanced performance on a vigilance task after glucose ingestion was prevented in subjects who were told that the drink contained only the non-nutritive sweetener, aspartame. Thus, expectations can clearly be important; indeed, Melanson *et al*. (1999) found that blood glucose levels after an aspartame-sweetened zero-energy drink were negatively correlated to the perceived sweetness of the drink.

Mechanistic implications

Given these inconsistencies, it is not surprising that a previous review of this literature up to 1994 (Rogers & Lloyd, 1994) concluded that the results of these studies were equivocal and that there was little compelling evidence for the beneficial effects of glucose administration upon the cognitive function of healthy individuals. Rather, Rogers & Lloyd (1994) suggested that the high baseline or rapidly rising levels of blood glucose, often observed in these studies to predict better performance, may reflect increased sympathoadrenal and adrenocortical activity, including an increase of plasma adrenaline, noradrenaline, and cortisol.

Glucose, sympathetic arousal and cognitive performance. There is considerable evidence that adrenergic arousal improves cognitive performance via peripheral β-adrenoceptor activation (McGaugh, 1989; Nielson & Jensen, 1994) as well as raising blood glucose (Gold, 1995). However, increased sympathoadrenal output raises blood glucose primarily via inhibition of uptake and disposal (Sherwin & Saccà, 1984), and there is no direct evidence that this is the mechanism underlying these glucose-related improvements in human performance. Adrenergic antagonists oppose the effects of arousal, but not glucose, on memory (Nielson & Jensen, 1994; Gold, 1995). Furthermore, it has been found that, whereas manipulating arousal levels by means of incentive motivation does produce selective improvements in performance, those improvements are unrelated to blood glucose levels (Green *et al*. 1997*a*). Indeed, sympatho-adrenal arousal during a psychologically challenging performance test does not necessarily lead to any change in plasma glucose in the absence of intake (Hagström-Toft *et al*. 1993).

Donohoe & Benton (1999*b*) hypothesised that an important methodological difference between studies in this area may be whether or not subjects were given a demanding task very soon after the glucose drink. They compared performance of groups with or without a demanding test immediately after either a glucose or placebo drink. Having to perform the demanding task improved subsequent word recall after a glucose drink, suggesting a possible interaction with adrenergic enhancement of memory. Importantly, however, this arousal effect was diminished in those subjects whose blood glucose was rapidly rising by 20 min. Insofar as the timing implies rapid absorption of glucose, we suggest one possibility is that these subjects were less aroused by the demanding test, and so performed worse subsequently, compared with subjects whose blood glucose was not yet rising. That is, in those latter subjects, glucose absorption may

have been delayed by greater arousal in response to the demanding task (Wing *et al*. 1985; Blair *et al*. 1991). Indeed, differing patterns of postprandial blood glucose changes have been associated with personality factors such as extraversion and introversion (Christie & McBrearty, 1979), which in turn could interact with perceived demands of the task. However, it should also be remembered that over-arousal might lead to poorer cognitive performance (Reid & Hammersley, 1999), and rising blood glucose could reflect less efficient cell uptake and disposal from the circulation (Kennedy & Scholey, 2000).

A further complication that can cloud interpretation is how recently subjects have eaten a meal before glucose loading and testing. A recent meal may interact with the impact of arousal on blood glucose as well as with the effect of further glucose intake (Martin & Benton, 1999). Moreover, fasting has been associated with enhanced speed of performance on memory tasks in some studies (Benton & Owens, 1993; Green *et al*. 1997*a*), but poorer recall levels in others (Martin & Benton, 1999).

In considering a possible role for arousal in mediating glycaemic effects on performance, it should be noted that ingestion of food, and even pre-ingestive sensory stimulation by food (Nederkoorn *et al*. 2000), will elicit acute sympathetic activation, at least partly to regulate blood pressure homeostasis during diversion of blood to the splanchnic bed (Lipsitz *et al*. 1993; Vaz *et al*. 1995). Glucose ingestion is no exception (Mathias, 1990; Kennedy & Scholey, 2000), whereas involvement of insulin release depends on the time of day (Biston *et al*. 1996). Cardiovascular responses to meals also depend on both meal size and time of day; heart rate and systolic blood pressure rose after a 1807 kJ (432 kcal) breakfast but not after a 531 kJ (127 kcal) breakfast, whereas these measures increased after both a 573 kJ (137 kcal) and a 5402 kJ (1291 kcal) lunch (Macht, 1996). Furthermore, afferent vagal nerve stimulation, for instance by absorbed nutrients or gastrointestinal hormones, is known to enhance memory retention in human subjects (Clark *et al*. 1999).

Nevertheless, Kennedy & Scholey (2000) found that heart rate increased further during cognitive performance testing, irrespective of whether glucose or a placebo drink had been ingested. Working memory performance was better in subjects with lower baseline heart rates (who had greater task-induced increases). Better pancreatic function may also be important, since a greater decline in blood glucose during the tasks, after glucose ingestion, was associated with better performance. However, other aspects of individual physiological efficiency and arousal responses need to be considered, as pre-task plasma glucose levels correlated positively with performance, whether or not glucose had been ingested (Kennedy & Scholey, 2000).

In addition, recent understanding of the use of lactate as fuel by neurones, and the importance of glycogen stores in astrocytes, suggests a more complex yet orchestrated relationship between arousal, glucose uptake and performance (Rennie, 2000). Astrocytic glycogen shows rapid turnover during euglycaemia, so is not a passive store, but an active supplier of energy substrate to neurones (Fillenz *et al*. 1999), as well as protecting neuronal survival during glucose deprivation (Ransom & Fern, 1997). Ide *et al*. (2000) have shown that, during high energetic demand such as when exercising (and perhaps during stress), the brain metabolises lactate from muscle and astrocytic glycolysis, then during recovery, rapid glucose uptake is stimulated to replenish depleted glycogen stores. Indeed, lactate infusion is known to ameliorate cognitive deficits during hypoglycaemia (Maran *et al*. 1994).

It is also now clear that the increase in glucose delivery by blood to the activated brain, accompanying increased regional cerebral blood flow, primarily results in uptake of the glucose by astrocytes, and storage as glycogen (very little of the increased available O is used at first) (Fillenz *et al*. 1999). That is, the extra glucose is not immediately used by neurones. The release of glucose to activated neurones from astrocytic glycogen, for instance during acute stress, is

probably controlled by the action of noradrenaline on astrocytic β-adrenoceptors (Fillenz *et al.* 1999). This astrocytic buffering effect on glucose and O use by neurones might underlie the improvement in delayed but not immediate recall seen after O_2 inhalation (Winder & Borrill, 1998); thus, it appears to be memory consolidation, not retrieval, that is improved by inhalation of O_2 (Scholey *et al.* 1998). Further, it has recently been proposed that deficient catecholaminergic control of this astrocyte-mediated neuronal energy regulation underlies impaired cognition in Attention-Deficit–Hyperactivity Disorder (Todd & Botteron, 2001). Therefore, it seems likely that many of the findings of studies relating glucose to cognitive performance reflect an interaction between physiological efficiency, glucoregulation, ability to cope with, and involvement in, stressful tasks, and brain function.

The one area where glucose administration is most strongly associated with improvements in cognition is in its application to groups who are nutritionally or metabolically 'at risk', such as the elderly (e.g. Parsons & Gold, 1992; Manning *et al.* 1993; Messier *et al.* 1997); for reviews, see Messier & Gagnon, 1996). Further support for this vulnerability can be seen in two studies which have directly assessed the relative effects of glucose administration in elderly and young, healthy adults (Hall *et al.* 1989; Manning *et al.* 1997). In both cases, it was found that the administration of a glucose drink selectively enhanced the memory performance of elderly subjects but not that of young, healthy subjects. However, this age difference may partly depend on the relative demands of the task; a glucose load can enhance performance in young adults given more demanding tests of memory and attention (Korol & Gold, 1998; Donohoe & Benton, 1999*b*). Other recent evidence emphasises the importance of individual glucose regulation in predicting a memory-enhancing effect of carbohydrate loading in the elderly; Kaplan *et al.* (2000) found that mashed potato and barley, as well as glucose ingestion, improved cognitive performance specifically in elderly subjects with poor baseline memory performance and poor pancreatic β-cell function. This effect was independent of changes in blood glucose.

Glucose, cortisol and cognition. One potential physiological mediator of an association between glucoregulation and cognition is the hypothalamic pituitary adrenal axis, and particularly the release of the glucocorticoid hormone, cortisol. There are several reasons to consider a link between cortisol and effects of glucose on cognitive performance. Performance on short-term memory (Brandenberger *et al.* 1980) and declarative memory tasks (Kirschbaum *et al.* 1996) has been found to be strongly inversely correlated to the size of cortisol rise induced by a challenging task. Moreover, acute administration of cortisol impairs performance on working memory (Lupien *et al.* 1999), declarative memory and spatial thinking tasks, but not procedural memory (Kirschbaum *et al.* 1996). These effects probably involve action of cortisol on hippocampal neuronal function; receptors binding cortisol are abundant in the hippocampus (De Kloet *et al.* 1993), a brain region strongly implicated in declarative memory (Newcomer *et al.* 1994). There is also evidence for rapid, non-genomic, membrane-receptor modulation of memory by glucocorticoids (Filipini *et al.* 1991), which might be involved here. In addition, glucocorticoids can inhibit glucose uptake into the hippocampus (Horner *et al.* 1990).

The typical rise in cortisol following a stressful psychological task was seen in subjects given a glucose load (100 g/400 ml) 1 h before the task, but not in fasted subjects (Kirschbaum *et al.* 1997). Furthermore, plasma glucose level after the load predicted the extent of stress-induced rise in cortisol, whereas in the absence of stress, cortisol did not change following the glucose load (Kirschbaum *et al.* 1997). This dependence of a stress-induced rise in cortisol on the non-deprived state might help explain improved performance on certain tasks in children who missed breakfast, and in overnight fasted adults, in whom speed of performance on

memory tasks was enhanced (Benton & Owens, 1993; Green *et al.* 1997*a*): perhaps those outcomes particularly benefited from a lack of cortisol release during the tests.

One possible resolution of these and earlier findings (e.g. where falling glucose or increased insulin secretion predicts better performance) may be that faster uptake and disposal of glucose (after a glucose load) would be associated with a smaller rise in cortisol during a stressful test of performance, and so would thus minimise cortisol-induced deterioration of memory. This is also in line with the accumulating evidence that poor glucoregulation, and physiological inefficiency, is associated with poor cognitive performance following glucose administration (Hall *et al.* 1989; Craft *et al.* 1994; Kaplan *et al.* 2000; Kennedy & Scholey, 2000). For instance, peak plasma glucose achieved after a glucose or placebo load has repeatedly been shown to predict poorer performance on memory tasks, even on days when no glucose load was given (Hall *et al.* 1989; Manning *et al.* 1990).

The critical interaction is likely to be between glucoregulatory processes and the impact of a challenging task; thus, glucose (or other food) ingested before a stressful challenge may promote cortisol secretion, the more so in vulnerable individuals with poor glucoregulation. By comparison, in overweight insulin-resistant subjects at rest (unstressed), both higher fasted and post-glucose-load blood glucose levels were associated with lower morning plasma cortisol levels after oral glucose load (Fernández-Real *et al.* 1997). Such subjects are also likely to show greater cortisol responses to stress (Rosmond & Björntorp, 2000).

The interaction of glucoregulation, cortisol and cognitive performance might also mediate earlier findings of relationships between personality type and effects of meals on performance (Smith, 1992). More direct evidence is needed, since associations between personality variables and cortisol are complex (Pruessner *et al.* 1997); but positive coping strategies have been found to predict lower cortisol responses to stress (Bohnen *et al.* 1991). Furthermore, when cortisol release is elicited by a stressful task before a midday meal, the cortisol response to the meal is suppressed in proportion to the amount of cortisol released during the pre-meal stressor (Brandenberger *et al.* 1980). This has implications for interpretation of pre- and post-meal changes in performance. For instance, it might explain the resistance of anxious subjects to a post-lunch dip in performance (Smith, 1992), if the impact of the meal on cortisol was lessened in those subjects by prior cortisol release.

Glucose, cholinergic neural function and memory. Other work in this area has centred on the hypothesis that the effects of glucose administration mostly benefit memory function (for example, see Gold, 1986). This is a hypothesis which is consistent with findings of beneficial effects of glucose on the performance of tasks which, whilst not primarily being measures of memory capacity, have high concurrent processing (or working memory) loads (for example, see Kennedy & Scholey, 2000). One possible mechanism underlying this effect may be related to the role played by glucose in the synthesis of the neurotransmitter acetylcholine (Gold, 1995), which work in the field of Alzheimer's dementia has identified as being associated with memory (for example, see Fibiger, 1991). Together with dietary choline, the co-substrate for synthesis of acetylcholine is acetyl CoA, which is in part a by-product of glucose metabolism.

However, whereas glucose availability can influence acetyl CoA production, the systemic or central synthesis and release of acetylcholine clearly will not simply depend on plasma glucose; for cholinergic enhancement of memory by glucose availability, complex and specific mechanisms would need to be invoked. Glucose-enhanced release of central acetylcholine may depend on increased activity of cholinergic neurones, as during demanding tests of learning and memory. For instance, glucose injection in rats further enhances hippocampal release of acetylcholine stimulated by task performance, whereas no such effect is seen in resting rats (Korol & Gold, 1998).

The psychological effects of dieting to lose weight

Dieting to lose weight is one of the most common food choice-related behaviours undertaken in the developed world. To illustrate this point, it is estimated that, at any one time, 12 % of women between the ages of 12 and 64 are following a weight-loss programme (Gregory *et al.* 1990) and that 90 % have attempted weight-reducing diets at some time in their lives (Ogden, 1992). Although the effects of acute food deprivation (at least in terms of missing individual meals or deprivation for periods of up to 24 h) are outlined see p. 171, there is also a body of evidence which indicates that more self-induced attempts at weight control by means of energy reduction are associated with a range of negative psychological impairments. Whilst it is certain that extreme cases of self-induced starvation such as those characteristic of anorexia nervosa result in impairments of neuropsychological function (for example, see Fox, 1981), it is generally considered that these impairments result from the gross changes in brain anatomy (such as ventricular enlargement and sulcal widening) which accompany extreme starvation (for example, see Kingston *et al.* 1996).

In contrast non-psychopathologically induced attempts at weight reduction are also associated with psychological problems. Dieting to lose weight has been associated with swings in mood state (Tiggemann, 1994), depression (Smoller *et al.* 1987) and increased concern with body shape (Warren & Cooper, 1988; Green & Rogers, 1993).

Dieting has also been associated with impaired cognition (Wing *et al.* 1995). For example, female dieters performed more poorly than non-dieters on a task of sustained attention (Rogers & Green, 1993), as well as poorer performance on immediate free recall and simple reaction time tasks (Green *et al.* 1994). In addition, this study found that motor performance (as assessed by two-finger tapping speed) was actually better in dieters than non-dieters, indicating that these effects could not be explained in terms of a simple slowing of overall motor speed or lack of motivation amongst dieters. Further, performance has been demonstrated to be poorer, within the same individuals, when dieting than when not dieting (Green & Rogers, 1995), indicating that the phenomenon is related to dieting *per se*, rather than pre-existing individual differences between dieters and non-dieters. Interestingly, this study is notable for two further aspects. First, the impairments in performance were found even amongst those dieters who reported not having lost any weight over the course of the diet and, second, that the impairments were most marked in those who had been dieting for the shortest period of time. These two factors combine to suggest that the dieting-related phenomenon is psychological, rather than physiological in nature, a hypothesis that will be elaborated upon at a later point in the present review.

Further work has attempted to fractionate the nature of the deficit in cognitive function associated with the attempt to lose weight by means of dieting. Rather than representing a global deficit, it has been demonstrated that the cognitive processing deficit associated with naturalistic, uncontrolled dieting is fundamentally a deficit of 'working memory' (Green *et al.* 1997*b*). Working memory (Baddeley, 1986) can be conceptualised as being the fundamental cognitive processing system, in that it serves to allocate limited cognitive processing capacity to other ongoing cognitive operations in order of their relevance or importance to an individual. In addition, it has been found (Green & Rogers, 1998) that the magnitude and precise structure of these deficits is comparable to those which result from the preoccupying cognitions characteristic of high levels of anxiety (for example, see Darke, 1988) and clinical depression (for example, see Channon *et al.* 1993).

This latter finding, in conjunction with the finding that dieters have impairments in cognitive function in the absence of any significant weight loss over the course of the diet (Green & Rogers, 1998), leads to the conclusion that these deficits are psychological in nature. They may

be best explained in terms of a threshold hypothesis of the impact of intrusive, task-irrelevant, thoughts on cognitive processing efficiency. Non-dieting, restrained eaters are characterised by an enduring preoccupation with body shape (Herman & Polivy, 1980) which can be assumed to impose some capacity restraint on working memory. When combined with the state-related feelings of hunger and food craving resultant from the reduced energy intake experienced during attempted weight loss (Hart & Chiovari, 1988), it is hypothesised that a threshold of preoccupation is crossed, whereby insufficient working memory capacity is available to perform efficiently the tasks presented to dieters in experimental settings. This hypothesis is supported by studies which have demonstrated no clear effects of weight loss upon cognition in the absence of any pre-existing concerns with weight and body shape (for example, see Deijen *et al.* 1989; Kretsch *et al.* 1997; Shukhitt-Hale *et al.* 1997). The central conclusion which can be drawn from this work, therefore, is that the cognitive load imposed by food cravings and hunger (in addition to pre-existing concerns with body shape and self-esteem) in dieters is a causal factor in their impaired cognitive task performance. One potential problem with such a hypothesis is the finding that highly restrained eaters (and dieters are, by definition, restrained eaters) do not experience significantly more food cravings than unrestrained eaters (Hill *et al.* 1991). However, rather than weighing against this hypothesis, this finding serves to outline the conceptual and practical distinction between high levels of dietary restraint and actual dieting behaviour outlined by Lowe (1993). Whilst high levels of restraint are a necessary precondition of starting and maintaining a diet, it is not necessarily the case that an individual will be on a diet if they are a restrained eater. Hill *et al.* (1991) present no information on the current dieting status of their subjects.

Although there are a number of studies (cited above) which tend to support this hypothesis, there is some evidence that experimentally induced weight loss negatively affects cognitive function. Wing *et al.* (1995) reported that the administration of a low-carbohydrate diet (2297 kJ (549 kcal)/d) over 28 d amongst obese subjects was associated with impaired performance on a trail-making task, relative to a group administered a low-fat diet (2469 kJ (590 kcal)/d). This interpretation can, however, be criticised on several grounds. Foremost of these is that, although β-hydroxybutyrate levels (a metabolic indicator of starvation) rose significantly over the whole 28 d of the diet, trail-making task performance was only significantly impaired at 7 d of dieting, compared with baseline. Subsequent measurements showed that trail-making performance after 28 d of low-carbohydrate dieting was actually better than at baseline. This was further confounded by marginally significant baseline differences between trail-making performance. More recent work has also indicated that simple weight loss *per se* may not be a fully adequate explanation for the impairments in cognition found amongst naturalistic dieters. Buffenstein *et al.* (2000) found that a 6-week weight-reducing diet (3347 kJ (800 kcal)/d) was associated with impairments in simple reaction time, although choice reaction time was actually improved amongst participants subjected to this regimen.

The evidence presented so far has supported the conclusion that dieting-related impairments in cognition result from psychological factors, rather than the gross consequences of food deprivation. It is still possible, however, that some of the more subtle physiological consequences of food deprivation may play a mediating role in this phenomenon. The most widely investigated of these possible mechanisms concerns that of a dieting-related change in serotoninergic neurotransmitter function, possibly resulting from lowered plasma TRP : LNAA impairing 5-HT synthesis (see p. 178). There is evidence that moderate chronic lowering of plasma TRP : LNAA, by dieting (e.g. 4184 kJ (1000 kcal)/d) for up to 3 weeks (Anderson *et al.* 1990), selectively enhances brain 5-HT receptor function in women (though not in men) (Goodwin *et al.* 1987; Walsh *et al.* 1995; Cowen *et al.* 1996).

There are, however, at least three potential problems with such an argument. The first of these concerns the order of magnitude of TRP depletion produced by the two methods outlined see pp. 178 and 192, i.e. TRP-deficient amino acid preloads or restricted energy intake. In general, the amino acid drink method tends to deplete TRP by some 70 to 80 % (for example, see Park *et al.* 1994). The diet method, however, tends to deplete plasma TRP by roughly 10–20 % (for example, see Cowen *et al.* 1996; Wolfe *et al.* 1997). It is, therefore, uncertain whether naturally occurring dieting would reduce TRP sufficiently to affect cognitive processing efficiency; the dietary regimen imposed in these studies is somewhat more severe than that of most typical weight-loss diets, with a daily energy intake of 4184 kJ (1000 kcal). The second concern is that previous studies which have demonstrated dieting-related impairments in cognition have found these deficits even in dieters who have not reported any weight loss over the course of their diet (Green & Rogers, 1995). Further, it has been demonstrated that a similarly restrictive weight-loss regimen administered over a 15-week period produces no significant impairment of cognitive function (Kretsch *et al.* 1997). Third, animal studies show that acute starvation increases 5-HT synthesis and turnover in the brain, while longer-term starvation promotes 5-HT availability at the synapse by down-regulating presynaptic 5-HT re-uptake sites (Huether *et al.* 1998).

Serotoninergic function may also be affected in dieters by methods other than that of a simple reduction in TRP intake resulting from energy restriction. One of the most common weight loss strategies undertaken by dieters is an alteration in the fat : carbohydrate of the diet, with dieters eating a greater proportion of carbohydrate-rich foods (for example, see Tepper *et al.* 1996). Such foods, if very low in protein and eaten after fasting, might increase central 5-HT synthesis acutely. However, that is unlikely to account for the impaired cognitive performance, since it has been found that a carbohydrate-rich diet actually improves some task performance, albeit only in neurotic subjects (Markus *et al.* 1999). Nevertheless, a diet particularly low in some fats might impair cognition (see p. 180; Fischer *et al.* 2001).

Although these are powerful arguments against a simple serotoninergic explanation of the impairments in cognition found amongst dieters, they remain, as yet, unproven by published experimental evidence. Even if future work fails to confirm this hypothesis, it may very well be the case that other nutritional (rather than psychological) variables may mediate the phenomenon of impaired cognitive function in weight-loss dieting. For instance, there is some suggestion that plasma haemoglobin concentrations mediate task performance during experimentally controlled weight loss (Kretsch *et al.* 1998). In this case, however, the argument outlined above as to whether experimentally controlled weight loss is a good model for naturalistic dieting behaviour can still be raised.

Cholesterol levels and cognitive function

Aside from the previously mentioned negative psychological effects of attempted weight loss, there is a body of literature indicating that other dietary changes, such as attempts at lowering cholesterol levels, are similarly associated with psychological impairments. Reductions in plasma cholesterol levels are a major health goal for the Developed World, as it is seen as an essential factor in the prevention of CHD (AHA/Medical Scientific Statement, 1997) and ischaemic strokes. Nevertheless, a number of studies indicated that low or decreasing levels of cholesterol are associated with increased rates of death from suicide (for example, see Gallerani *et al.* 1995), incidence of depression (Glueck *et al.* 1994) and impaired cognitive function (in terms of choice reaction time; Benton, 1995). There is also some cross-sectional data to suggest

that higher cholesterol levels are associated with better cognitive function (Muldoon *et al.* 1997). It is the case, however, that these findings are inconsistent, with some studies finding no relationship between low cholesterol levels and depression (for example, see Strandberg *et al.* 1993).

It should be remembered that these studies are cross-sectional in nature, with the resultant difficulty in inferring causality. There are, however, two recently published clinical intervention trials which have demonstrated that the active reduction of cholesterol levels, either by means of dietary or pharmacological intervention, exerts negative psychological effects. Wardle *et al.* (2000) administered two forms of a 12-week dietary intervention to hypercholesterolaemic patients (one designed to lower overall plasma lipid levels, one designed to alter the intake ratio of monosaturated and polyunsaturated fats to saturated fats, and a non-intervention control group). It was found that, although mood state and a number of other markers of psychological wellbeing improved in all three groups, performance on a cognitively demanding measure of the ability to sustain attention was relatively impaired in the two lipid-lowering diet groups relative to the untreated control group. Further, performance on this task was found to correlate significantly with change in plasma cholesterol levels over the course of the intervention. Another study (Muldoon *et al.* 2000) found that a pharmaceutical cholesterol-lowering intervention (Lovastatin, administered at a dosage of 20 mg/d for a period of 24 weeks) impaired performance on a range of measures of cognitive function in subjects with hypercholesterolaemia. Specifically, it was found that the group who were administered the cholesterol-lowering drug failed to display the practice-related improvement in performance characteristic of the placebo-administered group on tasks measuring vigilance, psychomotor speed and mental flexibility. In addition, although there were no significant correlations between change in task performance and change in cholesterol levels (as found by Wardle *et al.* 2000), there were significant correlations between final assessment levels of task performance and final assessment cholesterol levels. As with the Wardle *et al.* (2000) study, there were no significant changes in other markers of psychological wellbeing associated with Lovastatin. Taken as a whole, therefore, these two studies appear to indicate that the active attempt to reduce plasma cholesterol levels, whether by pharmacological or dietary means, is associated with negative cognitive outcomes.

One mechanism which has been hypothesised to underlie these effects centres on the role of cholesterol in maintaining the integrity of the lipid bi-layer of which cell walls are constructed. Although this hypothesis is discussed at greater length elsewhere (Kaplan *et al.* 1997), a brief summary follows. It is hypothesised that alterations in plasma cholesterol levels structurally affect the fluidity of cell membranes, including neurones. In the case of neurones, alterations in membrane fluidity will have implications for neurotransmitter and synaptic function. Indeed, there is evidence to suggest that the cholesterol content of surrounding plasma influences the cell membrane phospholipid to cholesterol mole ratio, this being an indirect measure of membrane fluidity (McMurchie & Patten, 1988). It has been further hypothesised that one of the neurotransmitter systems particularly affected by alterations in plasma cholesterol concentrations may be that of 5-HT. This is supported by evidence that (*in vitro*) 5-HT receptor binding can be increased or decreased as a function of the addition or removal of cholesterol from brain synaptic membranes (Heron *et al.* 1980). Since 5-HT is implicated in a wide range of psychological phenomena, from frontal lobe function to arousal levels and appetite control, any reliable effects exerted by cholesterol on 5-HT function may be expected to demonstrate profound psychological effects.

Interestingly, it has recently been proposed that serotoninergic deficits related to neuronal membrane fluidity may reflect the balance of *n*-3 and *n*-6 essential fatty acids (Hibbeln *et al.*

1998). It is suggested that cholesterol levels could be a marker for variation in these essential fatty acids, which have been linked to cognitive impairment and psychopathology (Youdim *et al.* 2000).

Age-related cognitive decline and vitamin status

There is a large body of evidence which indicates that vitamin status is an important mediator in the maintenance of efficient cognitive processing. It is a common finding that psychological function decreases with age. The impairments in memory associated with ageing can lead to inattentiveness, poorer judgements and planning ability, slowed reaction times and impaired information processing (Craik *et al*. 1995), leading to an increased vulnerability to accidents. This has obvious implications for health care, since the elderly consume a disproportionately large proportion of health care resources than would be predicted from their numbers in the population as a whole. It is also the case that a major determinant of the quality of life for elderly individuals is the efficiency of their mental processes. Although the decline in mental abilities of healthy individuals is slight before the age of 70 years, some groups seem particularly at risk. For instance, elderly inactive isolated individuals (so-called 'disengaged home makers') have shown substantial declines in cognitive function during longitudinal studies (Sternberg, 1986). Whilst decline in mental abilities is, of course, associated with dementia, this does not appear to be an identifiable cause of the loss of cognitive processing abilities for many individuals. There is some doubt as to whether these declines represent a natural, inevitable function of the ageing process or are due to small pathological changes in the brain resulting from conditions accompanying ageing. It has, for instance, been suggested that the decline in cognitive function which accompanies normal ageing is largely attributable to secondary factors such as disordered sleep patterns, alcohol consumption, elevated serum cholesterol, raised blood pressure, diabetes and reduced cerebral blood flow (Rinn, 1988). These are factors which, to varying degrees, have a nutritional component.

Several Department of Health surveys carried out between 1968 and 1979 revealed problems of vitamin deficiency amongst the elderly population in the UK. Although the proportions vary according to each survey, it has been consistently found that large numbers of free-living elderly individuals over 70 years of age suffer from deficiencies in a number of vitamins. For instance, a substantial portion of the elderly living in the UK experience deficiencies in riboflavin, cobalamin (vitamins B_2 and B_{12}) and serum folate. It is possible that these sub-clinical deficiencies are a factor in the cognitive decline observed with ageing.

B-complex vitamins, folate and neural function

A number of vitamins have functional utility in the maintenance of the central and peripheral nervous system. Deficiencies in the B-vitamin group (thiamin, B_2, B_6, B_{12} and folate) have been linked with conditions such as irritability, depression, peripheral neuropathy (both B_6 and B_{12}; Rosenberg & Miller, 1992) and myelin degeneration (Rosenberg & Miller, 1992). One possible route whereby deficiencies in these vitamins may affect cognition relates to their role in the metabolism of the S amino acid homocysteine. Plasma levels of homocysteine have been variously inversely correlated with levels of B_{12} (Koehler *et al.* 1996; Lussier-Cacan *et al*. 1996), vitamin B_6 and folate (Selhub *et al*. 1993). Indeed, serum concentrations of the homocysteine metabolite methylmalonic acid can be used as an indirect marker of B_{12} deficiency

(Lindenbaum *et al.* 1988). Elevated levels of homocysteine have been shown to be an important factor in the development of a number of vascular problems such as occlusive vascular disease, atherosclerosis and cerebrovascular disease (for an extensive review, see Ueland & Refsum, 1989). Importantly, it has been found that supplementation with a range of B-complex vitamins reduces serum homocysteine levels in both elderly (Koehler *et al.* 1996) and younger (Woodside *et al.* 1998) populations.

It is possible, therefore, that subclinical deficiencies of B-complex vitamins amongst the elderly UK population are a causal factor in the decline in cognitive processing efficiency amongst this group (this being either a problem of low intake or lowered absorption) and that the mechanism by which this occurs is raised homocysteinaemia. Indeed, there is evidence suggestive of a role for homocysteine-related neural damage in Alzheimer's dementia. McCaddon *et al.* (1998) found that Alzheimer's patients exhibited significantly higher plasma levels of homocysteine than non-demented controls and that, further, neuropsychological status was significantly related both to homocysteine and vitamin B_{12} levels. This finding has been replicated and extended by other groups (Lehmann *et al.* 1999), where it has also been found that, in addition to Alzheimer's patients, homocysteine levels are predictive of neuropsychological status in individuals suffering from other forms of dementia.

Although there are a number of published studies which have suggested links with vitamin status and cognitive performance amongst the elderly (for example, see Goodwin *et al.* 1983; Sommer & Wolkowitz, 1988; Bell *et al.* 1990; Riggs *et al.* 1996), these studies have been correlational in nature and have provided no clear hypothesis as to the mechanisms underlying these relationships. One intervention study, however, revealed no effect of supplementation on cognitive performance (Chome *et al.* 1986), although this can possibly be interpreted in terms of the low subject numbers and the relatively short period of supplementation (5 weeks). Stronger evidence can be seen in the results of Deijen *et al.* (1992), who demonstrated significant improvements in cognitive function following vitamin B_6 supplementation in a larger sample of healthy, self-supporting men aged between 70 and 79 years. The evidence for a definite role for B-complex vitamins in the cognitive function of the elderly remains, therefore, mostly suggestive (albeit strongly so).

Antioxidant vitamins and cerebrovascular health

It has also been proposed that cognitive impairment might be prevented or significantly delayed by increased intake of antioxidants in the diet, such as vitamins C and E (for example, see Kalmijn *et al.* 1997; Lethem & Orrell, 1997). This view is based on various lines of evidence.

Biochemical and physiological studies implicate oxidative damage to the central nervous system microvasculature in the aetiology of neurodegenerative diseases, including Alzheimer's disease (Richardson, 1993; Thomas *et al.* 1996). At the same time, oxidative modification of LDL is probably a critical component of the atherosclerotic process (Witztum, 1994), and there is a well-established link between the prevalence of dementia and the presence of one or more E4 alleles of the apolipoprotein E gene (Bondi *et al.* 1995; Rubinsztein, 1997). The apolipoprotein E gene produces apolipoprotein E which is involved in, among other things, transporting cholesterol in the blood and neuronal repair (Rubinsztein, 1997).

More directly, several studies have demonstrated significant relationships between cognitive functioning in the elderly and antioxidant nutrient intake or status. Gale *et al.* (1996), for example, reported an association between cognitive impairment and both low intake and plasma levels of vitamin C, and also between cognitive impairment and increased risk from

ischaemic stroke. These authors specifically suggested that vitamin C status may influence cognitive function in elderly people through an effect on atherogenesis. Another study (Ortega *et al.* 1997) found significant relationships between cognitive functioning, measured using the Mini Mental State Examination, and some ten dietary-intake variables. Included among these were intakes of vitamin C, β-carotene, folate and Fe (positive associations), and intakes of monounsaturated fatty acids, saturated fatty acids and cholesterol (negative associations). Vitamin E status has also been specifically linked with memory function (Perkins *et al.* 1999). Conversely, however, Kalmijn *et al.* (1997) found no significant relationships between intakes of the potential antioxidants vitamins C and E, β-carotene and various flavanoids, and either cognitive impairment or cognitive decline in elderly men, again assessed with the Mini Mental State Examination, which is a measure of overall neuropsychological function. This lack of a relationship between vitamin E and cognition has also been replicated by Jama *et al.* (1996).

Of course, without additional information, conclusions cannot be drawn about cause and effect from correlational studies. One published intervention trial, however, revealed significant correlations between vitamin C levels, mood, performance on measures of memory and attention and global neuropsychological status in elderly individuals after 12 months of supplementation with a range of antioxidant vitamins (Smith *et al.* 1999*b*). Clear interpretation of the results of this study is, however, made difficult by two facts. First, the fact that cognitive function did not significantly change over the course of the supplementation period. Second, the reported significant correlations between vitamin status and psychological status were not adjusted for the effect of multiple comparisons and, if this statistically appropriate procedure were carried out, these effects would probably disappear. Nevertheless, there is sufficient evidence to suggest that studies of the effects of antioxidant supplementation may well yield positive outcomes for cognitive functioning (Lethem & Orrell, 1997). This includes the possible involvement of other mechanisms, such as dietary modification of immune function, whereby, for example, vitamin E could be expected to influence the development of arteriosclerosis (Meydani *et al.* 1998). The finding that there is an association between the apolipoprotein E4 genotype and dementia also suggests that potentially protective dietary interventions could be targeted for high-risk groups. Again, this conclusion is speculative.

Summary

We have reviewed the potential nutritional influences on cognitive function and arousal, excepting severe malnutrition for which substantial literature exists. New developments in understanding dietary influences on neurohormonal systems, and their implications for cognition and affect, allow reinterpretation of both earlier and recent findings.

The methods and outcomes of numerous studies, and inferred mechanisms, are disparate and diverse, so generalisations are difficult. Nevertheless, some cautious predictions can be made; with due allowance for circadian rhythms, acute effects of meals on both cognition and arousal can be observed. Breakfast can improve cognitive function, though not universally, and most evidently in young and nutritionally vulnerable children. The composition of meals may be more influential than meal size or timing, particularly when substantial nutritional variations from habitual meals are encountered. Acutely, carbohydrate-rich–protein-poor meals are more likely to be sedating and anxiolytic, while inducing lapses of sustained attention: by comparison, protein-rich meals may be arousing, enhancing reaction time but also unfocused vigilance. These acute effects may vary with current nutritional state, time of day, and temperament. Chronically, protein-rich diets have been associated with decreased positive and increased

negative affect relative to carbohydrate-rich diets. Evidence continues to accumulate that these effects may be mediated by diet-induced changes in monoamine neurotransmitter activity, functioning of the hypothalamic pituitary adrenal axis and cortisol secretion.

Fat-rich meals can reduce alertness after a delay, especially where they differ from habitual fat intake. This might be mediated by CCK release. Even so, manipulation of fat intake produced few consistent effects on performance. Effects of pure fat intake may be less disruptive to performance than either pure carbohydrate or protein, perhaps because of relatively benign neurohormonal responses.

It is argued that many of these effects should be interpreted in the context of idiosyncratic response to challenging, often stressful, tests of performance. A case in point is the change in performance after administration of glucose, which may depend on the amount of sympathetic activation, glucocorticoid secretion and pancreatic function, reflecting the glucoregulatory ability of the individual. This argument is supported by recent evidence of astrocytic buffering of changes in cerebral glucose supply, which is susceptible to acute stress. That is, behavioural effects of glucose ingestion should not be seen as resulting from simple fuelling of neural activity.

Thus, the outcomes can often be predicted by vulnerabilities based on individual differences in coping with stressful challenges, interacting with nutritional history. For instance, anxious introverts are less susceptible to a 'post-lunch dip' in performance, as well as being protected from stress-induced deterioration in mood by prior consumption of high-carbohydrate–protein-poor meals. Again, there is evidence that these effects may be mediated by nutritionally sensitive neurohormonal processes. Functioning of such systems may also be susceptible to dietary influences on neural membrane fluidity, such as cholesterol and/or essential fatty acid levels.

Women who diet to lose weight appear vulnerable to cognitive impairment; the evidence suggests that preoccupying thoughts during dieting reduce working memory capacity, impairing performance independently of weight loss.

Finally, the elderly, often nutritionally 'at risk', may be particularly susceptible to diet-dependent cognitive decline. There is increasing evidence for a key role for the B-complex vitamins, and vitamins C and E, particularly in protecting against cognitive impairment resulting from deteriorating cerebrovascular integrity.

Future research should aim to extend this integration of earlier and recent findings, so that the full implications of dietary influences on cognition and arousal can be understood. Then, efficient strategies can be employed that will benefit the nutritional and neuropsychological health of susceptible individuals.

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