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ORIGINAL INVESTIGATION

Rachael T. Donohoe · David Benton

Cognitive functioning is susceptible to the level of blood glucose

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Abstract *Rationale:* It is traditionally assumed that under normal conditions the brain is well supplied with glucose, its basic fuel. However, given the limited stores of glucose in the brain and its dependence on a continual peripheral supply of glucose, it was considered whether the availability of glucose, and the ability to efficiently utilise glucose, affects cognitive functioning. *Objective:* There is increasing evidence that the provision of blood glucose influences memory. To date, the impact of blood glucose on non-memory task performance has received little attention. The present study investigated whether the performance of non-memory tasks was susceptible to the level of blood glucose. Two studies are reported in which the influence of a glucose containing drink on six cognitive tests was considered. *Results:* The consumption of a glucose containing drink resulted in faster performance on the Porteus Maze and greater Verbal Fluency. Higher levels of blood glucose on arrival at the laboratory were associated with better performance on the Water Jars test. With both the Porteus Maze and Block Design tests, after taking a glucose drink, poor performance was associated with blood glucose that remained at higher levels. *Conclusion:* It was suggested that we should consider two physiological mechanisms, firstly, that an equilibrium develops between plasma and brain glucose, such that those with higher levels of blood glucose could be expected to have higher levels of brain glucose and secondly, whether there are individual differences in the efficiency with which glucose is taken from the blood; those with poor glucose control perform some cognitive tasks more poorly.

Key words Block design · Blood glucose · Embedded figures · Frontal lobes · Glucose · Logical reasoning · Memory · Porteus maze · Verbal fluency · Waters jars

R.T. Donohoe (✉) · D. Benton
Department of Psychology, University of Wales Swansea, Swansea SA2 8PP, Wales, UK
e-mail: psdonoh@swansea.ac.uk

Introduction

It has been traditionally assumed that the brain is well supplied with glucose, its basic fuel, and its functioning is not influenced by normal variations in the level of blood glucose (Booth 1994). However, there is increasing evidence that exogenous sources of glucose, and individual differences in blood glucose regulation, influence memory (Gonder-Frederick et al. 1987; Hall et al. 1989; Benton and Owens 1993; Benton et al. 1994), although other aspects of cognition have been relatively ignored.

In both young and aged rodents, glucose administration has been associated with enhanced memory (Gold 1986, 1991, 1992). A similar phenomenon has been found in elderly humans (Gonder-Frederick et al. 1987; Hall et al. 1989) and Alzheimer patients (Manning et al. 1993). More recently, this research has been extended to healthy young adults (Benton and Owens 1993; Benton et al. 1994). To date, the relationship between blood glucose and non-memory tasks has received limited attention. The aim of the present paper was to consider whether aspects of cognitive functioning, other than memory, were susceptible to the provision of blood glucose. Two studies are presented that extend previous reports by examining the influence of a glucose containing drink on six cognitive tasks that do not rely primarily on memory.

The few studies that have looked beyond memory have examined the impact of blood glucose on attention. In both adults (Moser et al. 1983; Benton et al. 1994; Benton 1990) and children (Benton et al. 1987), a glucose drink has been found to improve the ability to sustain concentration. The number of errors made in a driving-simulator was found to decrease when a glucose drink was consumed (Keul et al. 1982). Benton et al. (1994) reported that low blood glucose levels were associated with a larger Stroop effect. The report that performance on the Stroop test, a task sensitive to frontal lobe damage (Stuss and Benson 1984), was susceptible to blood glucose suggested that it may be profitable to look

beyond memory and attention to other aspects of cognition. The present study, therefore, examined the influence of blood glucose on frontal lobe functioning. When examining the impact of frontal lobe damage, one of the most frequently mentioned features of the resulting behaviour is a lack of flexibility (Walsh 1978). If the provision of blood glucose is having minor effects on the functioning of the brain, and for this reason influences cognition, then a possibility that should be considered is that low blood glucose levels are associated with rigid rather than flexible thinking.

Experiment 1: influence of blood glucose levels on the logical reasoning, embedded figures and water jars tests

Introduction

Although the concept of flexibility/rigidity has been frequently used to summarise the behavioural changes that are associated with brain damage, the term is used in different senses; as a dimension of personality, a characteristic of perception and as a tendency to display stereotyped behaviour or to perseverate. Chown (1959) noted that there is no convincing evidence that rigidity represents a single aspect of behaviour. The present study examined the influence of blood glucose levels on two of these types of measure: the extent that individuals are influenced by set (Water Jars task) and perceptual flexibility (Embedded Figures). A test of logical reasoning was administered to see if blood glucose levels influenced another measure of higher level processing.

Materials and methods

Subjects

Sixty-seven female undergraduates, mean age 21.8±5.1 years, received a payment of £3 for participation. All had eaten their normal breakfast of at least 100 kjoules. The procedure was approved by the local ethics committee and the subjects gave written informed consent.

Water jars test. The test was based on the "Water-Jar Einstellung" test (Luchins 1942) and consisted of a series of arithmetic problems. The subject was faced with three water jars (labelled A, B and C) each of a known capacity. By adding and subtracting the volumes of the three jars the subject was required to create a new specified volume. The first five problems could only be solved using the method B–A–2C: for example, given three jars with volumes of 50, 81 and 7 obtain a volume of 17. All stages of the arithmetical problem had to be written. The intention of these first five problems was to establish a "set". The next four problems, labelled "Critical", were similar but could be solved with the previously used B–A–2C solution, or alternatively by either A–C or A+C. For example, when given jars with volumes of 21, 51 and 9, and asked to obtain 12, both the long and short solutions are possible. The data reported are the times taken to solve the Critical problems.

Embedded figures test. The version selected for this experiment was the Finding Embedded Figures Test (Thompson and Melacon 1990), which correlates highly with the Witkin Embedded Figures task (Melacon and Thompson 1989), but as it is more difficult it is better suited to a university population. The test consists of 35 embedded figures problems, each of a multiple choice format. The task was to find a smaller figure that is embedded in one of five larger, more complex, figures. The task was designed to ensure that it could not be finished in the 10 min allocated. The test score was calculated by subtracting the number of incorrect solutions from the number of correct solutions.

Logical reasoning test. The Baddeley Logical Reasoning Task (Baddeley 1968) was modified by the addition of new comparisons. A typical example is: if M is smaller than C tick false – Cm. Subjects were required to respond to each statement by ticking "true" or "false". However, if a conditional statement did not describe the two letters correctly, no tick was made. The test score was calculated by subtracting the number of incorrect solutions from the number of correct solutions. The test lasted for 5 min and could not be finished in this time.

Blood glucose. Blood glucose levels were measured using an ExacTech sensor (Medisense Britain Limited). The sensor uses an enzymic method that, coupled with microelectronic measurement, has been shown to be accurate (Matthews et al. 1987).

Glucose drinks. The glucose drinks consisted of 50 g glucose powder dissolved in a mixture of 250 ml water and two tablespoons of Robinson's Whole Orange Squash (sugar free). Two teaspoons of lemon juice were added to make the drinks less sweet. Placebo drinks contained the same ingredients, with the exception of the glucose powder, which was replaced with 3 g Sweetex, a low calorie sweetener containing aspartame and saccharin (Crookes Health Care Ltd). The drinks were identical in colour and taste and could not be distinguished by the subjects. Drinks were randomly allocated to subjects using a double-blind procedure.

Procedure

Blood glucose levels were measured at the start of the experiment. Following their normal breakfast, subjects consumed either a glucose or placebo drink. After 20 min, blood glucose levels were measured again. Subjects then performed the Water Jars, Embedded Figures and Logical Reasoning tests in this order. A final blood glucose level was then determined about 50 min after taking the drink. Testing occurred between 0900 and 1300 hours.

Statistical analysis

Three blood glucose measures were examined. The level on arrival is described as the baseline value. The change in blood glucose from baseline to that 20 min after consumption of the drink (prior to testing) was calculated. Similarly the change in blood glucose levels from 20 min to the end of the study (while performing the tasks) was calculated. The changes in blood glucose for placebo and glucose drinkers were considered separately, as the levels of blood glucose reflect markedly different experimental conditions.

Blood glucose criterion groups were created by selecting, arbitrarily, those who were in the top and bottom thirds of the distribution, and the performance of those in the top and bottom groups was contrasted. High and low baseline blood glucose criterion groups consisted of those subjects whose blood glucose levels were greater than 4.9 mmol/l (5.56±0.39 mmol/l; n=20) or less than 4.1 mmol/l (3.61±0.33 mmol/l; n=21) on arrival in the laboratory.

When the change in the level of blood glucose prior to testing was considered, placebo drinkers were allocated to the rising criterion group if their blood glucose levels increased by at least 0.51 mmol/l (1.41±0.67 mmol/l; n=10). They were contrasted with those whose blood glucose levels fell by at least 0.11 mmol/l (–0.20±0.56 mmol/l; n=12). Glucose drinkers were selected for

the rising criterion group if their blood glucose levels rose by 2.60 mmol/l or more (3.37±0.71 mmol/l; *n*=12) and were contrasted with those whose blood glucose levels fell or increased by no more than 1.80 mmol/l (1.26±0.63 mmol/l; *n*=11).

When the change in blood glucose while performing the tests was considered, placebo drinkers were allocated to the rising criterion group if their blood glucose levels either rose or fell by no more than 0.19 mmol/l (0.15±0.16 mmol/l; *n*=11). They were compared with those whose blood glucose levels fell by more than 0.80 mmol/l (–1.23±0.43 mmol/l; *n*=12). Glucose drinkers were selected for the rising criterion group if their blood glucose levels increased or fell no lower than 0.09 mmol/l (0.87±0.87 mmol/l; *n*=10) and were contrasted with those whose blood glucose levels fell by at least 1.40 mmol/l (–2.14±0.79 mmol/l; *n*=11).

The effects of baseline and changing blood glucose levels on performance were analysed using two-way ANOVAs: baseline level (high/low) or change in blood glucose (rising/falling)×dependent variable (Critical problem solving time, Embedded Figures score or Logical Reasoning score). One-way ANOVAs examined the influence of type of drink on performance: drink (placebo/active)×dependent variable. Interactions were further explored by the calculation of simple main effects.

Results

When the blood glucose levels were examined the Drink×Time interaction reached significance [$F(2,130)=30.09$, $P<0.001$]. At baseline, the blood glucose levels did not differ (4.5±0.7, 4.4±0.8 mmol/l). However, after 20 min (6.9±1.3 cf. 4.9±0.9 mmol/l, $P<0.001$), and also at the end of the experiment (6.1±1.44 cf. 4.5±0.8 mmol/l, $P<0.001$), those who had consumed the glucose drink had higher levels of blood glucose.

Effect of drink

The type of drink consumed did not influence the time taken to solve the Water Jars task [$F(1,65)=0.09$, n.s.], Logical Reasoning test [$F(1,65)=2.09$, n.s.] or Embedded Figures scores [$F(1,52)=1.89$, n.s.].

Effect of blood glucose levels

A significant main effect of baseline blood glucose on Water Jars task performance was found [$F(1,39)=5.68$, $P<0.022$]. As shown in Fig. 1, subjects with a higher level of blood glucose solved the Critical problems significantly faster than those with a lower blood glucose level.

Baseline blood glucose levels did not influence either Logical Reasoning [$F(1,39)=0.02$, n.s.] or Embedded Figures scores [$F(1,30)=0.13$, n.s.].

Changing blood glucose prior to testing did not effect the performance of placebo or glucose drinkers on the Water Jars [placebo – $F(1,20)=0.56$, n.s.; glucose – $F(1,21)=0.19$, n.s.], Logical Reasoning [placebo – $F(1,20)=0.04$, n.s.; glucose – $F(1,21)=0.06$, n.s.] or Embedded Figures tests [placebo – $F(1,16)=0.04$, n.s.; glucose – $F(1,16)=0.01$, n.s.]. Similarly, changing blood glucose levels during testing did not effect Water Jars [placebo – $F(1,21)=1.31$, n.s.; glucose – $F(1,19)=0.10$, n.s.], Logical Reasoning [placebo – $F(1,21)=2.13$, n.s.; glucose – $F(1,21)=2.81$, n.s.] or Embedded Figures performance [placebo – $F(1,16)=0.75$, n.s.; glucose – $F(1,13)=0.45$, n.s.].

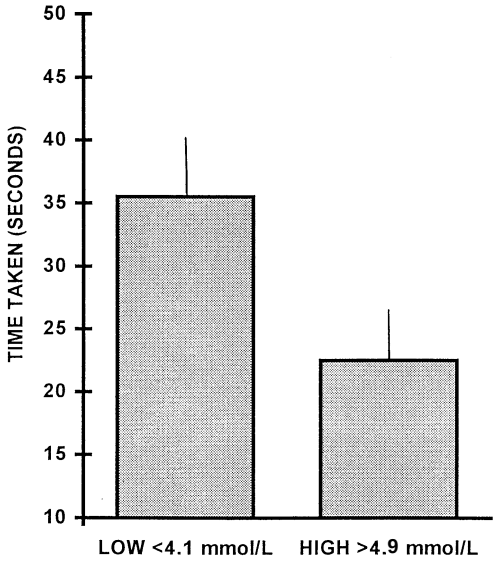

Fig. 1 The influence of baseline blood glucose levels on the water jars test. Those who had a higher level of blood glucose solved the Critical problems significantly faster than those with a lower blood glucose level. The data are mean±SE

Experiment 2: influence of blood glucose on verbal fluency, Porteus Maze and block design

Introduction

In this second study, the influence of blood glucose on the Porteus Maze, Block Design and Verbal Fluency tests was examined. It is known that these tests are particularly influenced by frontal lobe damage (Lezak 1983), an area of the brain necessary for a "supervisory attentional system" that produces a response to novelty that is planned rather than routine (Shallice 1982).

Materials and methods

Subjects

Sixty-nine female undergraduates, mean age 20.2±2.1 years, who each received a payment of £3, participated in this experiment. All subjects had consumed breakfast (over 100 kjoules).

Verbal fluency. In the Controlled Oral Word Association test (Benton and Hamsher 1976) the subjects were required to name as many words as possible, within 1 min, beginning with a given letter of the alphabet. Proper nouns, numbers and the same word with a different suffix were excluded. Unlike the other tests two alternative forms were available allowing the Verbal Fluency test to be administered as a repeated measure. The availability of two sets of letters matched for their frequency of use enables increased statistical power. Before taking a drink subjects responded to the letters C F L and 20 min after the drink to the letters P R W. The score was the sum of all acceptable words.

Block design test. In this sub-test of the Wechsler Adult Intelligence Scale, subjects were presented with a number of cubes. Each had two red, two white and two red and white sides. Using these blocks, the task was to reproduce designs of increasing complexity. The first five used four blocks. The first two were treated as practice; the mean times taken for the next three are the data reported as the easy problems. The next four problems required nine blocks. The first two were again treated as practice trials and the time taken to complete a final two trials are reported as the difficult problems.

Porteus maze. Mazes suitable for those aged 7–14 years and the adult maze of the Vineland Revision of the Porteus Maze were used (Porteus 1959). Subjects were instructed to complete the mazes at their own pace. However, to provide a sensitive measure of performance, and unknown to the subject, the time taken to complete each maze was recorded and is the measure reported. The time taken to complete the mazes for ages 7, 8 and 9 were combined, as were the times for mazes for ages 10, 11 and 12. Thus four measures were analysed, the time taken to perform mazes for ages 7–9, 10–12, 14 and the adult maze.

Blood glucose measurement and drinks. Details of drinks and blood glucose measurement are given in experiment 1.

Procedure

Blood glucose levels were measured at the start of the experiment. The first Verbal Fluency test was administered after which either a glucose or a placebo drink was consumed. After 20 min, blood glucose levels were again measured and the second Verbal Fluency test was administered. The Block Design test was taken followed by the Porteus Maze. Finally, a third blood glucose level was determined. Testing took place between 0900 and 1300 hours.

Statistical analysis

As in experiment 1, baseline and changing blood glucose criterion groups were created by selecting, arbitrarily, those who were in the top and bottom thirds of the distribution.

High and low baseline blood glucose criterion groups consisted of those subjects whose blood glucose levels were greater than 4.3 mmol/l (4.0±0.3 mmol/l; n=23) or less than 4.1 mmol/l (3.61±0.33 mmol/l; n=21) on arrival in the laboratory.

When changing blood glucose levels prior to testing were considered, placebo drinkers were allocated to the falling criterion group if their blood glucose levels fell by at least 0.14 mmol/l (–0.70±0.76 mmol/l; n=11). They were contrasted with those whose blood glucose levels rose by at least 0.30 mmol/l (0.86±0.40 mmol/l; n=11). Glucose drinkers were selected for the falling criterion group if their blood glucose levels either fell or increased by no more than 1.90 mmol/l (1.47±0.53; n=13) and were compared with those whose blood glucose levels increased by 2.90 mmol/l or more (3.47±0.45 mmol/l; n=12).

For consideration of the changes in blood glucose during testing, placebo drinkers were allocated to the falling criterion group if their blood glucose fell by at least 0.40 mmol/l (–0.95± 0.45 mmol/l; n=12). They were compared with those whose blood glucose levels increased or stayed the same (0.46±0.35 mmol/l; n=9). Glucose drinkers were selected for the falling criterion group if their blood glucose levels fell by at least 0.69 mmol/l (–1.48±0.94 mmol/l; n=12) and were contrasted with those whose blood glucose levels rose by 0.30 mmol/l or more (0.88± 0.31 mmol/l; n=11).

Two-way repeated measures ANOVAs examined the impact of baseline and changing blood glucose levels on performance: Blood glucose level (high/low, or rising/falling)×Porteus Maze times (years 7–9, 10–12, 14 and adult); or Block Design times (easy trials, difficult trials); or Verbal Fluency score (before drink, after drink). Similarly, two-way repeated measures ANOVAs examined the influence of type of drink on performance: Drink (placebo/glucose)×time taken or test score.

Results

When blood glucose levels were examined the interaction Drink×Time reached significance [F(2,134)=66.46, P<0.001]. Blood glucose levels did not differ at baseline

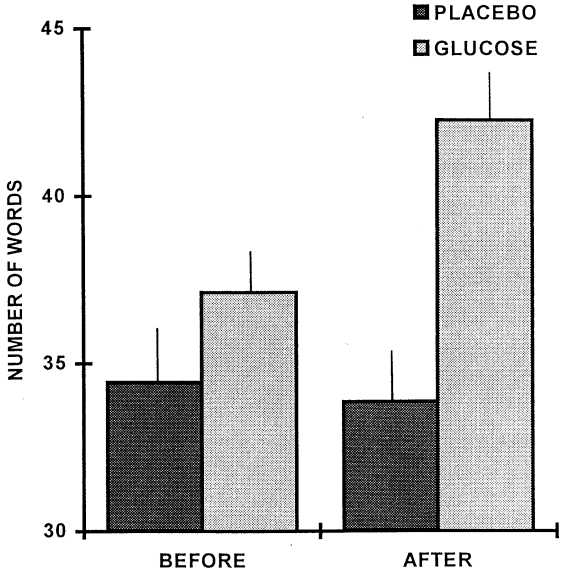

Fig. 2 The effect of a placebo or glucose drink on verbal fluency. Subjects who had taken a glucose drink generated significantly more words, 25 min after the drink, than placebo drinkers. The data are mean±SE. *Black bars* placebo, *grey bars* glucose

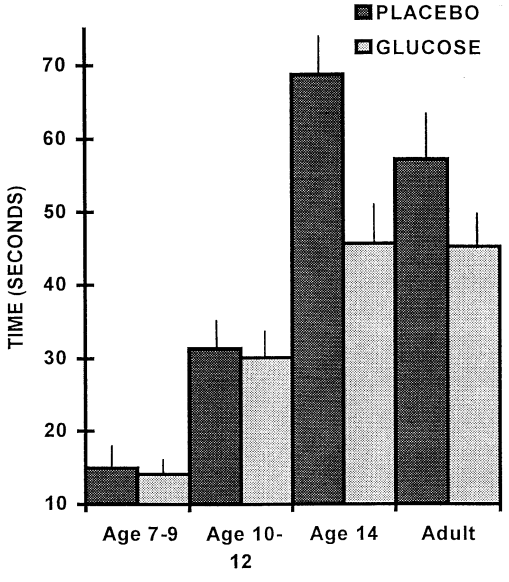

Fig. 3 The influence of a placebo or glucose drink on the porteus maze task. Glucose drinkers tended to complete both difficult mazes, age 14 and adult, significantly faster than placebo drinkers. The data are mean±SE. The data are mean±SE. *Black bars* placebo, *grey bars* glucose

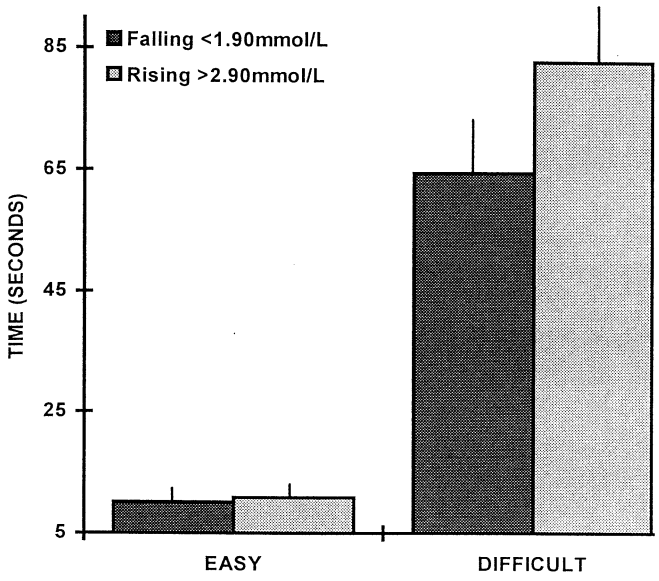

Fig. 4 The effect of changing blood glucose levels after a glucose drink on the block design test. Subjects whose blood glucose levels were falling after performance of the verbal fluency test completed the difficult designs significantly faster than those whose blood glucose levels were rising. The data are mean±SE. *Black bars* falling <1.90 mmol/l, *grey bars* rising >2.90 mmol/l

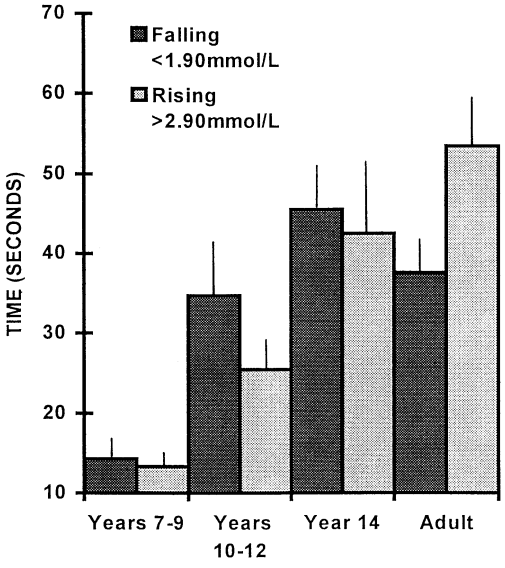

Fig. 5 The effect of changing blood glucose levels after a glucose drink on the Porteus maze task. Subjects whose blood glucose levels were falling after performance of the verbal fluency test completed the adult maze significantly faster than those whose blood glucose levels were rising. The data are mean±SE. *Black bars* falling <1.90 mmol/l, *grey bars* rising >2.90 mmol/l

(4.7±0.7 cf. 4.7±0.5 mmol/l). However, after 20 min (7.1±0.9 cf. 4.8±0.8 mmol/l, $P<0.001$), and at the end of the experiment (6.9±1.3 cf. 4.5±0.5 mmol/l, $P<0.001$), those taking the glucose drink had higher values.

Effect of drink

The consumption of the glucose drink did not influence performance on the Block Design task [$F(1,67)=0.27$, n.s.]. However, the Drink×Time interaction reached significance for Verbal Fluency [$F(1,67)=17.49$, $P<0.001$]. Figure 2 shows that although scores did not differ before taking the drink, the Verbal Fluency of those who consumed the glucose drink was greater 25 min following the drink ($P<0.001$).

The Drink×Trial interaction was also significant [$F(3,201) = 5.13$, $p<0.002$) when the Porteus Maze data were examined. Figure 3 shows that the time taken to solve the more difficult mazes tended to be faster in those who had consumed a glucose drink (age 14, $P<0.002$; adult, $P<0.08$).

Effect of blood glucose levels

The level of baseline blood glucose did not significantly influence Verbal Fluency [$F(1,42)=1.75$, n.s.], nor the times taken to solve the Porteus Mazes [$F(3,126)=0.78$, n.s.] and Block Designs [$F(1.42)=0.32$, n.s.].

Changing blood glucose levels prior to testing significantly influenced the performance of glucose drinkers on both the Block Design [$F(1,23)=4.28$, $P<0.05$] and the Porteus Maze tests [$F(3,69)=3.23$, $P<0.03$]. Figure 4 shows that those subjects whose blood glucose levels fell completed the difficult designs of the Block Design task significantly faster than those whose blood glucose levels rose ($P<0.02$).

Although Simple Main Effects failed to substantiate any significant differences in Porteus Maze performance, inspection of Figure 5 reveals a tendency for those subjects whose blood glucose levels fell to complete the difficult Adult maze faster than those whose blood glucose level rose.

Changing blood glucose levels did not significantly influence Verbal Fluency [$F(1,20)=0.20$, n.s.]. Placebo drinkers performance on all three tests was not significantly influenced by changing blood glucose levels.

Changing blood glucose levels during testing did not influence performance on the Block Design [placebo – $F(1,19)=0.02$, n.s; glucose – $F(1,21)=1.49$, n.s.], Porteus Maze [placebo – $F(1,19)=0.44$, n.s; glucose – $F(1,21)=0.01$, n.s.] or Verbal Fluency tests [placebo – $F(1,19)=0.03$, n.s; glucose – $F(1,21)=0.49$, n.s.].

Discussion

The influence of blood glucose levels on memory is well documented (see Introduction); the present study examined whether this phenomenon generalised to non-memory tasks. The performance of some, but not all, non-memory tasks were susceptible to the provision of blood glucose. The present and previous research of the association between blood glucose levels and aspects of cognition can be viewed as producing a relatively consistent

pattern. It is, however, necessary to distinguish baseline blood glucose levels from changes in blood glucose over time.

Firstly, there have been reports that a high level of baseline blood glucose was associated with better memory (Benton and Owens 1993; Parker and Benton 1995) and performance on a vigilance task (Benton et al. 1994). In the present study, a higher level of baseline blood glucose was associated with better performance on the Water Jars task (Figure 1). When an association between baseline blood glucose levels and subsequent performance has been reported, in every instance a higher level of blood glucose has been associated with better performance. As it is known that an equilibrium develops between plasma and brain glucose (Lund-Andersen 1979), those with initially high levels of blood glucose can be expected to have higher levels of brain glucose. Since the blood glucose levels observed in the present study were within the normal range (4.0–8.0 mmol/l; Cryer 1993), the findings are consistent with the suggestion that cerebral functioning may benefit from even small increases in blood glucose. These findings provide a practical implication for those administering standardised cognitive tests. Transient changes in blood glucose, such as those that occur after having consumed a meal, may affect performance. If, and what, subjects have eaten should be considered. Benton and Parker (1998) reported that subjects who had eaten breakfast had a better memory than those who had missed breakfast. In addition, the detrimental effects of fasting on memory were reversed by the consumption of a glucose drink.

Secondly, individual differences in the ability to deal with blood glucose account for other aspects of the data. Following a meal or drink, blood glucose levels typically rise for half an hour, after which they fall, returning to near baseline levels within approximately 2 h. Individual differences in blood glucose control determine the rate to which blood glucose levels return to baseline. There are several reports that better glucose control is associated with better performance. In the normal elderly (Gonder-Frederick et al. 1987; Hall et al. 1989; Craft et al. 1992) memory was better following a glucose drink, but only in those whose blood glucose levels returned to near baseline levels; those whose blood glucose levels continued to rise had poorer memory. A similar phenomenon was observed in aged rats; a negative correlation between the peak blood glucose response to glucose ingestion and inhibitory avoidance retention was reported (Stone et al. 1990). More recently, blood glucose control has been related to cognitive functioning in healthy young adults. A falling level of blood glucose, in those who had consumed a glucose drink, was associated with better memory, reaction times (Benton et al. 1994) and performance on a dichotic listening task (Parker and Benton 1995). In the present study, a fall in blood glucose following the glucose drink was associated with faster performance on the Block Design and Porteus Maze tasks (Fig. 4 and Fig. 5). If the assumption is made that with some cognitive tasks, but not others, the level of blood glucose in the brain limits functioning, the question arises as to the nature of the tasks that are susceptible to the level of available glucose. This question is addressed below.

How should the association between falling blood glucose levels and better cognitive functioning be interpreted? Although PET scans clearly demonstrate that increased cognitive functioning is associated with the rapid uptake of glucose from the blood to the brain (Reivich and Alavi 1983), it cannot be assumed that the association between the fall in blood glucose and better cognitive performance only reflects uptake by the brain. It is inevitable that the fall in blood glucose also reflects the peripheral uptake of glucose. The question arises as to whether the fall in glucose is anything other than a correlate between an enhanced metabolic rate induced by better motivation, that leads to better performance? Both heart rate and oxygen consumption have been reported to increase when subjects played a video game or performed mental arithmetic (Turner and Carroll 1985). Backs and Seljos (1994) found that as subjects responded to an increasing number of items in a memory task, metabolism and cardiorespiratory indices were stimulated.

Another possibility is that blood glucose levels may have fallen due to an anticipatory release of insulin associated with receiving a glucose drink. However, it has been reported that only mild activation of islet function, and thus insulin release, occurs in response to a meal stimulus, and this effect is largely limited to obese or anorectic individuals (Marks and Rose 1981). Furthermore, as the allocation of drinks in the present study was double blind, expectation would also have been present in placebo drinkers. In fact, the blood glucose levels of placebo drinkers remained relatively stable during the course of the two studies reported here.

Is there in fact any reason to believe that this fall in blood glucose, even in part, reflects an increased intake of glucose by the brain? There are a number of reasons to suggest that the supply of blood glucose acts on the brain to enhance functioning. PET scans demonstrate that cognitive demands inevitably increase the brains use of glucose (Reivich and Alavi 1983). Within minutes glucose from the bloodstream is metabolised selectively in those areas of the brain that are used for particular cognitive tasks. For this reason alone some of the decline in blood glucose will reflect the uptake of glucose by the brain. The report that in animals, a central injection of glucose enhanced memory, suggests that glucose has a central rather than peripheral action (Lee et al. 1988). Parker and Benton (1995) found that a decline in blood glucose preferentially stimulated the functioning of the left hemisphere, when performing a verbal task that is known particularly to increase glucose metabolism in the left hemisphere.

The nature of the supply of glucose to the brain makes it potentially susceptible to a limited supply particularly in demanding situations. The energy require-

ment of the brain is about 20% of the whole organism at rest, although its weight is only 2%. Strangely the energy stores in the brain are extremely small when compared with the high rate of glucose utilisation. Without renewal glucose reserves would be used up in about 10 min (Marks and Rose 1981); thus the brain is reliant on a continuous glucose supply.

Although some tests are susceptible to the level of blood glucose, others are not. Why are only some tests sensitive? A suggestion of heuristic value is that the "cognitive demand" induced by the task is critical. Before coming to a firm conclusion there is a need in future studies to examine the impact of systematically varying cognitive demand. Although it is difficult to quantify cognitive demand, the duration of the demand and its complexity could be considered. Previously the provision of blood glucose has been found to influence the difficult (incongruent) but not easy trials of the Stroop test (Benton et al. 1994); responses were faster on a choice, but not simple reaction time test (Owens and Benton 1994); it was the more demanding tasks that were susceptible to falling blood glucose. When the duration of a task was considered blood glucose influenced a vigilance task, but only towards the end of the test session (Benton 1990; Benton et al. 1994) and in a driving simulator only after driving 70 km (Keul et al. 1982). In the present study, it was the difficult rather than easy Porteus Mazes (Fig. 3 and Fig. 5) that were influenced. Similarly, with the Block Design tests, it was the difficult, rather than easy trials, that were susceptible to blood glucose (Fig. 4). The lack of a relationship between blood glucose and Logical Reasoning and Embedded Figures performance may, arguably, reflect the relatively limited demands placed on working memory by these tasks. It is possible that the influence of blood glucose on the performance of non-memory tasks may be limited to conditions of cognitive demand.

Given the clear evidence from PET studies that increased cognitive demand is associated with an increased use of glucose by the brain, it is perhaps not surprising that an increased supply of glucose benefits more demanding tasks. It is the finding that would be expected if there were individual differences in the ability to adequately supply local very active areas of the brain with glucose under demanding conditions.

Although traditionally most physiologists have believed that the brain was well supplied with glucose, resulting in a uniform concentration of extracellular glucose, this view is beginning to be challenged. The concentration of extracellular glucose varies with the strain of rat and the area of the brain examined (McNay and Gold 1999). In freely moving rats McNay and Gold (1997) showed a 25% decrease in hippocampal extracellular glucose during a spatial working memory task. An injection of glucose but not a placebo prevented this decline in extracellular glucose in the hippocampus. The assumption that the ability to transport glucose to particular areas of the brain never limits functioning may not stand examination.

Speculatively, the relationships between blood glucose and non-memory task performance may reflect an underlying influence of blood glucose on working memory. Previously, blood glucose levels were associated with enhanced performance on tests known to require central executive resources (Benton et al. 1994; Parker 1995). Parker (1995) reported that the performance of primary tasks specific to either the visuospatial scratch pad, or the articulatory loop, were not influenced by blood glucose. However, when a secondary verbal or spatial task was allocated, the disruption caused by overloading a slave system with a concurrent secondary task was significantly reduced in those subjects with a high level of blood glucose. This finding was interpreted as evidence that the provision of blood glucose did not influence the functioning of the slave systems, but was associated with enhanced central executive functioning.

It may be argued that the present associations between blood glucose and cognitive functioning are consistent with an influence of blood glucose on working memory, particularly the central executive mechanism. The Water Jars, Porteus Maze, Block Design and Verbal Fluency tests are frontal lobe tasks that require planning ability, and as such, would rely heavily on central executive resources (Rusted and Warburton 1991). The finding that the more difficult trials of these tests were susceptible to the level of blood glucose is consistent with an influence of blood glucose on the central executive mechanism.

The previous reports of an association between blood glucose and word list recall (Benton and Owens 1993; Benton et al. 1994) may also, tentatively, be accounted for by an influence of blood glucose on working memory. These studies used a supraspan word list that would require central executive resources. Further research is needed to determine whether glucose enhances cognition through a single mechanism responsible for the resource allocation for cognitive processing.

In conclusion, the present data suggest that in normal healthy individuals the provision of blood glucose influences the performance of some non-memory tasks. There is increasing evidence that we should question the assumption that, under normal conditions, the functioning of the brain is never influenced by fluctuations of blood glucose levels within the normal range. It should, however, be remembered that blood glucose is a single measure of a dynamic process and must be interpreted with care. The measurement of blood glucose may tell us little about the local glucose concentrations in particular sites in the brain. Changes in blood glucose levels are difficult to interpret as they can be expected to reflect both present and past cognitive demands as well as dietary history (Benton and Parker 1998).

References

Backs RW, Seljos KA (1994) Metabolic and cardiorespiratory measures of mental effort: the effects of level of difficulty in a working memory task. Int J Psychophys 16:57–68

Baddeley A (1968) A three minute reasoning test based on grammatical transformations. Psychonom Sci 10:341–342
Benton D (1990) The impact of increasing blood glucose on psychological functioning. Biol Psychol 30:13–19
Benton AL, Hamsher K de S (1976) Multilingual aphasia examination. University of Iowa, Iowa City
Benton D, Owens DS (1993) Blood glucose and human memory. Psychopharmacology 113:83–88
Benton D, Parker PY (1998) Breakfast blood glucose and cognition. Am J Clin Nutr 67:772S–778S
Benton D, Sargent J (1992) Breakfast, blood glucose and memory. Biol Psychol 33:207–210
Benton D, Brett V, Brain PF (1987) Glucose improves attention and reaction to frustration in children. Biol Psychol 24:95–100
Benton D, Owens DS, Parker PY (1994) Blood glucose influences memory and attention in young adults. Neuropsychologia 32:595–607
Booth D (1994) The psychology of nutrition. Taylor and Francis, London
Chown SM (1959) Rigidity – a flexible concept. Psychol Bull 56:195–223
Craft S, Zallen G, Baker LD (1992) Glucose and memory in mild senile dementia of the Alzheimer type. J Clin Exp Neuropsychol 14:253–267
Craft S, Dagogo-Jack SE, Wiethop BV, Murphy C, Nevins RT, Fleischman S, Rice V, Newcomer JW, Cryer PE (1993) Effects of hyperglycemia on memory and hormone levels in dementia of the Alzheimer type: a longitudinal study. Behav Neurosci 107:926–940
Cryer PE (1993) Glucose counter-regulation: the physiological mechanism that prevent or correct hypoglycaemia. In: Frier BM, Fisher BM (eds) Hypoglycaemia and diabetes. Edward Arnold
Gold PE (1986) Glucose modulation of memory storage processing. Behav Neural Biol 45:342–349
Gold PE (1991) An integrated memory regulation system: from blood to brain. In: Fredrickson RCA, McGaugh JL, Felten DL (eds) Peripheral signalling of the brain: role in neural-immune interactions, learning and memory. Hogrefe and Huber, Toronto, pp 391–420
Gold PE (1992) Modulation of memory processing: enhancement of memory in rodents and humans. In: Squire LR, Buttes N (eds) Neuropsychology of memory. Guildford Press, New York, pp 402–414
Gonder-Frederick L, Hall JL, Vogt J, Cox DJ, Green J, Gold PE (1987) Memory enhancement in elderly humans: effects of glucose ingestion. Physiol Behav 41:503–504
Hall JL, Gonder-Frederick LA, Chewning WW, Silveira J, Gold PE (1989) Glucose enhancement of performance on memory tests in young and aged humans. Neuropsychologia 27:1129–1138
Keul J, Huber G, Lehmann M, Berg A, Jakob EF (1982) Einfluß von Dextrose auf Fahrleistung, Konzentrationsfähigkeit, Kreislauf und Stoffwechsel im Kraftfahrzeug-Simulator (Doppelblindstudie im cross-over-design). Aktuelle Ernaehrungsmedizin 7:7–14
Lapp JE (1981) Effects of glycemic alterations and noun imagery on the learning of paired associates. J Learn Disabilities 14:35–38
Lee MK, Graham SN, Gold PE (1988) Memory enhancement with post-training intraventricular glucose injections in rats. Behav Neurosci 102:591–595
Lezak MD (1983) Neuropsychological assessment. Oxford University Press, London
Luchins AS (1942) Mechanization in problem solving. Psychol Mono 51:1–89
Lund-Andersen H (1979) Transport of glucose from blood to brain. Physiol Rev 59:305–359
Manning CA, Hall JL, Gold PE (1990) Glucose effects on memory and other neuropsychological tests in elderly humans. Psychol Sci 1:307–311
Manning CA, Ragozzino ME, Gold PE (1993) Glucose enhancement of memory in patients with senile dementia of the Alzheimer type. Neurobiol Ageing 523–528
Marks V, Rose FC (1981) Hypoglycaemia. Blackwell, Oxford
Matthews DR, Holman RR, Bown E, Steenson J, Watson A, Hughes S, Scott D (1987) Pen-sized digital 30-second blood glucose meter. Lancet 1:778–779
McNay EC, Gold PE (1997) Microdialysis measurement of brain extracellular glucose concentrations: basal levels and changes during behavioral testing in awake freely moving rats. Soc Neurosci Abstr 823:16
McNay EC, Gold PE (1999). Extracellular glucose concentration in the rat hippocampus measured by zero-net-flux: effects of microdialysis flow rate, strain and age. J Neurochem 72:785–790
Melancon JG, Thompson B (1989) Measurement characteristics of the finding embedded figures test. Psychol Schools 26:69–78
Moser L, Plum H, Buckmann M (1983) Der Einfluß von Dextrose auf die psychophysische Leistungsfähigkeit des Autofahrers. Aktuelle Ernaehrungsmedizin 8:247–249
Owens DS, Benton D (1994) The impact of raising blood glucose on reaction times. Neuropsychobiology 30:106–113
Parker PY (1995) The influence of blood glucose on the cognitive functioning of young adults. Doctoral thesis, University of Wales Swansea
Parker PY, Benton D (1995) Blood glucose levels selectively influences memory for word lists dichotically presently to the right ear. Neuropsychologia 33:843–854
Parsons M, Gold PE (1992) Glucose enhancement of memory in elderly humans: an inverted-U dose response curve. Neurobiol Aging 13:401–404
Porteus SD (1959) The maze test and clinical psychology. California, Pacific Books, Palo Alto
Reivich M, Alavi A (1983) Positron emission tomographic studies of local cerebral glucose metabolism in humans in physiological and pathological conditions. Adv Metabol Dis 10:135–176
Rusted JM, Warburton DM (1991) Molecules for modelling cognitive impairment. In: Hindmarch L, Hippius H, Wilcox G (eds) Dementia: molecules, methods and measures. Harwood Academic Publishers, London
Ryan C, Vega A, Drash A, Longstreet C (1984) Neuropsychological changes in adolescents with insulin-dependent diabetes. J Consult Clin Psychol 52:335–342
Shallice T (1982) Specific impairment of planning. Philos Trans R Soc Lond B 298:199–209
Stone WS, Wenk GL, Olton DS, Gold PE (1990) Poor blood glucose regulation predicts sleep and memory deficits in normal aged rats. J Gerontol 45:B169–173
Stuss DT, Benson DF (1984) Neuropsychological studies of the frontal lobes. Psychol Bull 95:3–28
Thompson B, Melacon JG (1990) Measurement characteristics of the Finding Embedded Figures test: a comparison across three samples and two response formats. Educ Psychol Meas 50:333–342
Turner JR, Carroll D (1985) Heart rate and oxygen consumption during mental arithmetic, a video game and graded exercise: further evidence of metabolically exaggerated cardiac adjustments. Psychophysics 22:261–267
Walsh KW (1978) Neuropsychology. Churchill Livingstone, Edinburgh