Psychopharmacology (1998) 137 : 259–270

ORIGINAL INVESTIGATION

J.K. Foster · P.G. Lidder · S.I. Sünram

Glucose and memory: fractionation of enhancement effects?

Received: 11 July 1997/Final version: 27 October 1997

Abstract Recent research findings indicate that glucose administration enhances some aspects of cognitive functioning. To date, those studies which have investigated the effects of glucose on memory in human participants have concentrated on its apparent ability to attenuate memory impairment. Relatively little research has been done in humans investigating the effects of glucose on memory performance in young healthy participants in whom no memory deficits exist. Moreover, the work which has been conducted in this population has produced somewhat equivocal findings. In this study, after overnight fasting the influence of a 25 g oral dosage of glucose on a range of measures of memory performance was investigated in healthy young female participants. Two control treatments (saccharin and water) were also administered. There was a significant glucose facilitation effect upon performance of long-term verbal free and cued recall tasks which did not vary with test delay. Performance on these free and cued verbal recall measures correlated significantly with blood glucose levels across all participants. No glucose-related facilitation was observed on either a test of short-term verbal memory (forwards/backwards digit recall) or a test of long-term non-verbal memory (complex figure reproduction). However, the significant glucose-related effects observed with long-term free and cued recall remained after controlling for participants' differential baseline blood glucose levels and individual levels of immediate memory performance. Therefore, memory improvement after glucose ingestion was not merely a consequence of lower baseline blood glucose or lower immediate memory performance in the glucose treatment group. These findings indicate that there may be some fractionation in the memory facilitation effects of glucose: the memory enhancing effect of glucose administration in healthy young adults may be greatest on tests of long-term verbal recall. The results suggest that glucose may enhance retention in and/or retrieval from long-term verbal memory.

Key words Glucose · Saccharin · Long-term memory · Short-term memory · Verbal memory · Non-verbal memory · Young control participants

J.K. Foster (✉) · P.G. Lidder · S.I. Sünram
Department of Psychology, University of Manchester, Oxford Road, Manchester M13 9PL, UK

Introduction

Over the past three or four decades, there has been increasing interest in the neurochemical regulation of memory. This field received a considerable impetus in the 1980s, with the identification of possible cognitive enhancing agents or "smart drugs". Many of the optimistic claims for these agents have proven ill-founded. However, empirical findings have established that increases in blood glucose levels subsequent to peripheral endocrine events may contribute towards the enhancement of memory storage processes (Wenk 1989; Gold 1991, 1992; White 1991). Glucose is the major source of energy for the brain and is essential to the normal functioning of the central nervous system (Sieber and Trastman 1992). Since relatively little glucose can be stored, the brain is reliant on a continuous supply of glucose as its primary fuel, delivered via the bloodstream. Glucose crosses the blood-brain barrier by facilitated transport (Wenk 1989) and it is utilized in a wide range of biochemical processes. For example, it is a substrate for the synthesis of the neurotransmitter acetylcholine, which has been widely associated with learning and memory (see Drachman and Leavitt 1974; Fibiger 1991; Hasselmo and Bower 1993 for reviews). Glucose has other important mechanisms of action in the central nervous system, including interactions with additional neurotransmitters

(e.g. dopamine, opiates). It also exerts influences on ATP energy utilization for fundamental brain processes such as ion transporter mechanisms. Moreover, glucose deprivation can severely disrupt neuronal activity, producing electroencephalographic (EEG) patterns characteristic of lowered cognitive functioning (Holmes et al. 1983).

Most of the information available about the role of glucose in cognitive functioning is derived from animal studies and from research into human memory deficits (see Messier and Gagnon 1996 for a recent review). For example, it has been frequently reported that memory functioning may deteriorate in the elderly (Gold 1986). Gold (1992) proposed that age-related diminution in cognitive function may be attributable to a decline in the endocrine response to stress which has been observed in older individuals. Salient environmental stimuli (for example, the perception of threat or reward) typically act as external stressors (White 1991). Ageing results in a depressed response from the adrenal glands to an external stressor, reducing the amount of adrenaline released (Hall et al. 1989). Adrenaline cannot cross the blood-brain barrier, but it is glycogenic and glucose may promote memory functioning (Wenk 1989; Gold 1991, 1992; White 1991). In clinical patients, the memory deficits observed in senile dementia of the Alzheimer type (SDAT) may be associated with an impairment in sympathetic activation of adrenal catecholamine release during cognitively demanding tasks, causing lowered blood glucose concentration (Craft et al. 1992).

In both humans and non-humans, poor glucose tolerance or abnormalities in glucose metabolism have also been associated with cognitive impairments. There is evidence from studies of ageing, age-related illnesses and diabetes that impaired glucose regulation may be associated with deficits in cognitive functioning, with particular emphasis placed on deficits in memory functioning (Perlmutter et al. 1984; Stone et al. 1990; Gradman et al. 1993; Meneilly et al. 1993; Ryan and Williams 1993). More generally, it has been suggested that blood glucose regulation may be a useful indicator of an individual's level of cognitive functioning (Holmes et al. 1983; Hall et al. 1989). In particular, a growing body of findings indicates that post-training blood glucose levels are associated with performance on subsequent tests of memory (Gold 1992). A peripheral mechanism has been identified, whereby glucose may also exert some indirect effects upon cognition via its own actions upon the liver (White 1991). However, the majority of work conducted has focused upon the direct actions of glucose on brain functioning (Gold 1992).

Additional evidence that glucose centrally regulates the storage of new information has accumulated from experiments in both humans and animals in which memory impairments have been attenuated by both central and peripheral administration of glucose. Glucose administration can enhance memory in elderly rats (Winocur 1995) and humans (Hall et al. 1989), and glucose can attenuate the amnesia induced in rats given scopolamine, a cholinergic antagonist (Wenk 1989). In addition, glucose administration significantly enhanced the performance of participants with SDAT on several tests of memory functioning: for example, orientation, word recognition, recall, narrative prose and word recognition (Manning et al. 1993).

Existing findings suggest that glucose enhancement of memory is characterized by an inverted-U-dose response curve, with the optimal dose for memory enhancement being approximately 25 g in elderly human participants (Parsons and Gold 1992). Not only does glucose improve memory recall when given either before or after training, but its retroactive enhancement outlasts the transient rise in circulating glucose levels following ingestion (Manning et al. 1992). It therefore seems unlikely that the glucose-induced facilitation of memory is merely a reflection of enhanced processing during encoding of target materials (Benton and Owens 1993). Rather, these findings imply that the administration of glucose participates in a chain of events which proceed after the target information has been encoded into memory (Gold 1992).

There is therefore considerable evidence now available to affirm the role which glucose plays in memory modulation. The extant literature indicates that glucose administration can attenuate some memory deficits, especially those associated with complex verbal declarative materials (see Messier and Gagnon 1996). In contrast, there have been mixed findings concerning the benefits upon memory of glucose treatment in healthy young participants, where no prior memory impairment exists. In a study of eighteen 19 to 25 year old human males, Azari (1991) reported no significant effect of glucose administration upon memory performance, and Cormier et al. (1993) failed to observe a glucose-related facilitation effect on memory in either young or elderly participants. By contrast, Hall et al. (1989) found that the extent to which glucose enhanced memory in young participants was less than that seen in their elderly counterparts, but that an effect was nevertheless observed. Benton and Owens (1993) reported a significant positive correlation between rising blood glucose values and recall of a 15-item word list in a group comprising all participants tested (i.e. those receiving glucose or placebo control). However, from amongst the wide range of different analyses of the data which were conducted, it was found that the type of treatment (glucose, control) did not affect the overall number of words recalled, nor did it affect performance on a spatial memory task or on recall of a story taken from the Wechsler Memory Scale – Revised (1987). In a subsequent study involving a similarly wide-ranging and complex series of analyses, Benton et al. (1994) reported that, in glucose drinkers (but not in placebo drinkers, in whom the opposite relationship appeared

to exist), a significant association existed between falling blood glucose in the period prior to hearing a word list and immediate recall. All other correlations between blood glucose concentration and level of recall performance (immediate, delayed) were non-significant. In this second study, the drink consumed (glucose, placebo) again did not influence the total number of words recalled, and neither the primacy nor the recency effects were differentially affected by glucose treatment. Apart from the inconsistent pattern of the data obtained in these two studies (Benton and Owens 1993; Benton et al. 1994), further problems concern the rather ad hoc nature of the arguments advanced to explain the findings and the somewhat arbitrary and inconsistent criteria applied across studies to define whether blood glucose levels are substantially rising or falling.

There is therefore some uncertainty and lack of clarity concerning the effects of glucose on memory in young healthy adults. This may be partially accounted for by the notion that some of these participants may already be working at optimal physiological and cognitive efficiency (and therefore functioning at or near a ceiling level of performance), whereas elderly participants and clinical patients are unable to achieve optimal performance due to age- or illness-related degenerative changes. If this is the case, any benefits of glucose on human memory in the young are most likely to be observed only when participants are engaged in sufficiently demanding cognitive tasks.

The purpose of the experiment reported here was to test the hypothesis that glucose administration may enhance memory performance in young healthy participants. More specifically, we were interested in evaluating which forms of memory, if any, are significantly facilitated by glucose administration. In the healthy elderly, evidence suggests that glucose has its largest effect upon declarative memory (Gold 1992). For example, Hall et al. (1989) found in elderly participants that glucose administration significantly enhanced performance on the Wechsler memory scale. This facilitation effect was especially noted on performance of the logical memory subtest, which evaluates declarative long-term memory. In younger participants, glucose facilitated memory performance on the digit span forward test only, performance on which was also facilitated in the elderly group (Hall et al. 1989). However, in a recent review, Messier and Gagnon (1996) argue that glucose preferentially improves performance on complex verbal declarative long-term memory tests such as the Wechsler Logical Memory scale. There is also therefore some uncertainty in the glucose literature concerning the nature of any facilitation effect observed in control participants. In this study, we therefore examined both different types of memory material and different subtypes of memory domain, evaluating performance on tests of i) verbal short-term memory, ii) non-verbal long-term memory and iii) long-term verbal declarative memory, in order to assess whether there was selectivity in any memory enhancement observed following administration of glucose.

To summarize, in this study a selection of memory tasks was performed by a panel of healthy control participants in order to evaluate whether glucose administration facilitates memory performance in young participants with no history of brain damage. We focused on a test of long-term verbal memory, given previous indications in the literature that glucose administration most reliably facilitates long-term verbal declarative memory (Messier and Gagnon 1996). However, we also administered tests of short-term memory and non-verbal long-term memory in order to determine the selectivity of any memory enhancement effect. It was assumed that a memory facilitation effect would be more likely to appear if participants' performance levels were constrained so that they lay below ceiling or near ceiling levels, and steps were taken in the running of the study to ensure that this was the case.

Materials and methods

Research participants

All participants were healthy undergraduates at the University of Manchester. Only females were tested in order to exclude possible gender-related differences. There were 30 participants in total, with ten per treatment group. Participants were between 18 and 22 years old (mean age = 19.5 years). It was ensured prior to testing that none of the participants was diabetic.

Materials

Memory tests

(i) Modified version of CVLT (Californian verbal learning test): evaluated immediate, short delay and long delay long-term memory (free recall, cued recall, recognition) for a supraspan word list (Delis et al. 1987).
(ii) Rey-Osterrieth complex figure drawing: evaluated long-term memory for non-verbal materials (Osterrieth 1944).
(iii) Forwards/backwards digit span: evaluated working memory span (Wechsler 1981, 1984).

Blood glucose equipment

(i) Medisense Exactech Companion blood glucose sensor (Medisense Britain Ltd., 16/17 The Courtyard, Gorsey Lane, Coleshill, Birmingham B46 1JA, UK).
(ii) Blood glucose test strips (Medisense Britain).
(iii) Automatic lancing device (Medisense Britain).
(iv) Disposable lancets (Medisense Britain).
(v) Rusco Pharmaceuticals pure powdered glucose.
(vi) Thornton & Ross saccharin tablets.

The accuracy and consistency of the Medisense blood glucose sensor has been examined by Matthews et al. (1987). In their evaluation, they found the device to be very accurate ($r = 0.98$) and consistent ($r = 0.92$).

Treatments

Participants received one of three possible treatments:

(i) Glucose – 25 g dissolved in 300 ml water.
(ii) Saccharin – 37.5 mg dissolved in 300 ml water (sweetness matched to dose of glucose).
(iii) Water – 300 ml.

Glucose was the treatment under investigation, saccharin was the control for possible sweetness reinforcement effects and water acted as an absolute control treatment. A 25-g dose of glucose was administered in the water, since evidence from the extant literature suggested this to be a suitable dosage to produce memory enhancement in control participants (Parsons and Gold 1992). Saccharin (37.5 mg) was used since, when dissolved in 300 ml water, the sweetness obtained was equivalent to that of the glucose solution. A volume of 300 ml was chosen as the optimal volume of liquid to be ingested. (A smaller volume would have caused the glucose solution to be unpleasantly sweet, whereas if the volume had been any greater, the time taken to consume the liquid would have been problematic.)

Design

The experiment followed a between-participant design, i.e. performance between the three different treatment groups was compared, with ten participants per treatment group.

Procedure

Each participant was required to attend one testing session which lasted approximately 45 min. Participants were notified that they should not eat after midnight prior to testing and should drink only water during this time. All tests were carried out between 0900 and 1200 hours using a double blind procedure. Participants were informed that they would undergo cognitive testing relating to human memory performance, and that they were required to drink a non-harmful, non-intoxicating liquid. Participants were neither informed of the nature of the liquid nor of the fact that three possible treatments were available. The three treatments (glucose, saccharin and water) were randomly allocated to participants as they volunteered for participation in the experiment. This was in order to ensure there was no bias in the level of knowledge about the experiment in the three different treatment groups. Treatments were administered immediately after the first, baseline blood glucose reading had been taken. No more than 5 min elapsed between participants starting to ingest the liquid (glucose solution, saccharin solution or water) and the start of testing.

Prior to the start of the study, the experimental procedure was approved by the Ethics Committee of the Department of Psychology, University of Manchester. In addition, all participants agreed to have their blood glucose levels monitored. Individuals were permitted to withdraw without prejudice if they were not willing to have small samples of their blood taken during the experiment. Before testing commenced, each participant had their baseline blood glucose concentration measured. In addition to the baseline reading, blood glucose measurements were taken 20 min and 40 min after the drink had been consumed. Blood glucose readings were obtained using the ExacTech blood glucose monitoring equipment, following the recommended procedure. The normal range in blood glucose concentration for human blood in the fasting condition is 3.9–5.6 mmol/l.

During each test session, three types of memory trial were performed:

(i) modified CVLT;
(ii) digit span (forwards and backwards);
(iii) Rey-Osterrieth complex figure.

Modified CVLT

The adult version of the CVLT comprises several subsections, namely:

Immediate free recall list A (five trials) (IFRa). A list of 20 words was read aloud to the participant. The list consisted of commonly used words belonging to one of four semantic categories. There were five words in each category. The categories were: tools, fruits, spices and herbs, clothing. The list was modified from the standard CVLT in that one additional item was added to each of the categories used. This was done in order to avoid the possibility of a ceiling effect occurring in healthy, intelligent, young participants if the standard version of the test had been used. The immediate free recall component of the test consisted of five trials. In each trial, the list was read with a word frequency of one word every 2.5 s. At the same time as the list was read to participants, they were required to perform two types of complex hand motor sequences. This was done to divide the participant's allocation of cognitive resources between the hand sequence and memory tasks, thereby further reducing the probability of the participant performing at ceiling on the memory task. The word list for the memory task was presented by tape so that the experimenter could monitor the participant's performance on the motor task. Participants were not told which task was the more important for the purposes of the experiment. Rather, they were told that they should perform to the best of their ability on each of the two tasks.

There were two different motor sequences. Each motor sequence was performed synchronously with both hands. Sequence 1 comprised "fist"-"chop"-"slap". Sequence 2 consisted of "back-slap"-"chop"-"fist". Each participant was required to complete one sequence between successive words on the list. Participants were also instructed to change between the two sequences every fifth word; i.e. sequence 1 = words 1–5, sequence 2 = words 6–10, sequence 1 = words 11–15 and sequence 2 = words 16–20. Participants were not told the number of words in the list, just instructed to change between sequence every fifth word. Additionally, they were informed that they would not be signalled as to when they should change but should themselves keep track of the number of words that had been read. After the list had finished, participants terminated the hand movements and verbally reported back as many items as they could remember from the list. They were not required to remember the words in any specific order, and no time limit for recall was imposed.

The word list test was repeated five times in succession without pause. Since there were 20 words in the list, and the list was read five times, the maximum cumulative score was 100. Scores on immediate free recall trials provide global measures of supra-span learning and immediate recall of information using self-generated cues.

Immediate free recall list B (one trial) (IFRb). This was the interference list. Participants were read a new list of 20 words belonging to one of four new semantic categories: fish, kitchen items, fruit, spices and herbs. Note that two of these categories are the same as for immediate free recall of list A, although there was no duplication of individual items across the two lists. Words were read at a frequency of one word per 2.5 s. No interference hand movements were performed. The list was read once only, after which participants verbally recalled as many of the items as they could remember from list B. The scores on immediate free recall of list B provide another measure of immediate recall of information using self-generated cues. A low score on list B compared with trial 1 list A indicates a high degree of proactive interference on list B from list A.

Short delay free recall (SDFR). Participants were asked verbally to recall as many of the items as they could remember from list A. Short delay free recall performance reflects the ability of the

participant to retain verbal information over a short period of time and retrieve that information using self-generated cues. A low score relative to acquisition scores indicates a high degree of forgetting during the delay and/or retroactive interference from the learning of list B on list A.

Short delay cued recall (SDCR). Participants were asked verbally to recall as many items as they could from list A using the names of the four semantic categories as cues for retrieval. Short delay cued recall performance reflects the ability of the participant to retain verbal information over a short period of time and retrieve that information using explicitly presented cues. A significant improvement of cued recall performance over free recall performance is typically observed, indicating a facilitation in performance with the presentation of explicit retrieval cues.

Long delay free recall (LDFR). This was the same as SDFR, but followed a 20-min delay after completion of the SDCR test. Long delay free recall performance reflects the ability of the participant to retain verbal information over a significant period of time and retrieve that information using self-generated cues. A low score relative to the short delay free recall score indicates a high degree of forgetting during the long delay.

Long delay cued recall (LDCR). This was the same as SDCR, but following a 20-min delay after completion of the SDCR test. Long delay cued recall performance reflects the ability of the participant to retain verbal information over a significant period of time and retrieve that information using explicitly presented cues.

Long delay recognition (LD recognition). Participants were read a list of 44 words containing all of the words in list A, some of the words in list B and several other interference words. The participant was required to respond 'yes' if they recognized a word as belonging to list A, and 'no' if they did not. Accurate recognition performance indicates retention of an item from list A, which may be preserved in long-term memory even though it may not have been successfully recalled in either the previous free or cued recall conditions.

Forward digit span

Participants were read a sequence of digits, comprising two sequences of identical length in each set. The shortest sequence comprised four numbers, while the longest sequence was nine digits long. After hearing each sequence in a set, the participant was required immediately to recall that sequence in the same order as they had heard it. Correct recall of each sequence was awarded one point. If either of the sequences in each set was correctly recalled, participants progressed to the next set, which consisted of number sequences one digit longer than the previous set. If participants failed correctly to recall either sequence pair in a set, the test was terminated. There were six sets each worth a possible two points. Therefore, the maximum possible score was 12. Digits were read at a frequency of one number per second.

Backward digit span

The procedure was the same as for the forward recall except participants were required verbally to recall the sequence in reverse order: i.e. if the sequence was 4-2-6-5, the participant was required to respond 5-6-2-4. The shortest sequence was three digits long, while the longest sequence comprised eight digits. The maximum possible score was again 12, and digits were once more read at a frequency of one number per second.

Rey-Osterrieth complex figure

Participants were presented with the Rey-Osterrieth complex figure (see Fig. 1). They were instructed to copy the diagram at their own pace and no time constraints were placed upon their completing the task. Thirty minutes later, they were asked to redraw the diagram from memory. Again, no time limits were imposed. The test was marked against the initial figure presented for copy, as per the standard marking procedure. For this purpose, the figure was broken down into 18 composite features each worth two points.

The sequence of testing was as illustrated in Fig. 2.

Statistical tests

The results of all the tests were subject to statistical analysis. Initially an ANOVA was performed to examine whether group performances were significantly different. For IFRa, the interaction between treatment and trial was also examined. For SDFR versus LDFR and SDCR versus LDCR, the interaction between treatment and delay was also evaluated. Significant effects revealed by ANOVA were analyzed further using the Studentized Range Statistic (q).

In addition, covariate analyses were performed in order to control for initial blood glucose levels and immediate memory performance on other group differences. This was done by conducting further ANOVAs in which each of these factors in turn was used as a covariate.

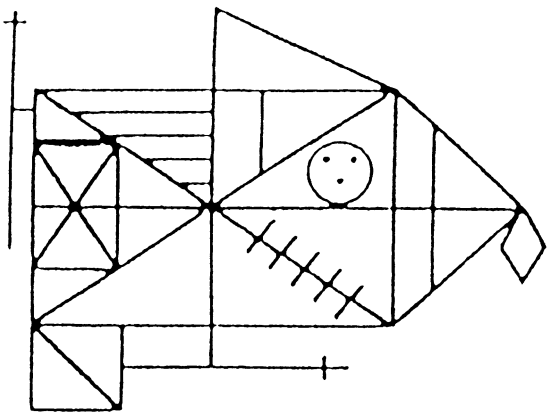

Fig. 1 The Rey-Osterrieth figure

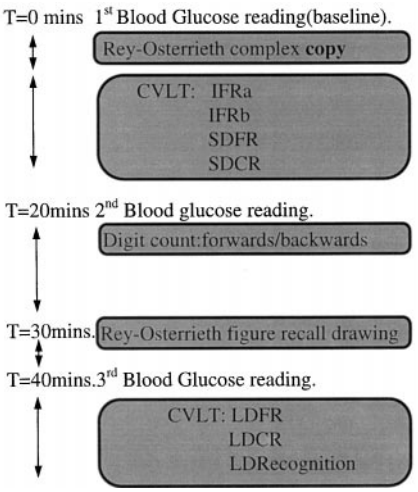

Fig. 2 Sequence of blood glucose and psychological testing during the experiment

Correlations were also performed in which memory performance was compared against blood glucose concentration (at the time of glucose measurement closest to test administration) in all participants, irrespective of their treatment. Finally, partial correlations were computed between memory performance and blood glucose concentration, with immediate memory performance partialled out (in order to provide a second control for level of immediate memory functioning).

Results

Blood glucose concentrations (BGCs)

At t0 (before ingestion of the treatment liquid) there were no significant differences between the group mean baseline BGCs. Following ingestion of the treatment liquid, there was a significant difference in group mean BGCs [$F(2,27) = 9.91$, $P < 0.01$] at both t20 and t40 (see Fig. 3). Post hoc analyses of the results (using the Studentized Range Statistic, q) indicated that there was no significant difference in the blood glucose levels for the two control groups, saccharin and water. However, at both t20 and t40, the BGCs of the glucose group were significantly greater than those of the two control treatments (a) t20: [$q(G,S)(2,87) = 4.74$, $P < 0.01$], [$q(G,W)(3,87) = 6.39$, $P < 0.01$]; (b) t40: [$q(G,S)(2,87) = 5.87$, $P < 0.01$], [$q(G,W)(3,87) = 6.96$, $P < 0.01$].

Memory tests

Overview

It was found that there was a significant difference in the performance of the three groups on four of the seven tasks, namely: SDFR, SDCR, LDFR and LDCR of the CVLT (see Fig. 4 and Table 1). On all

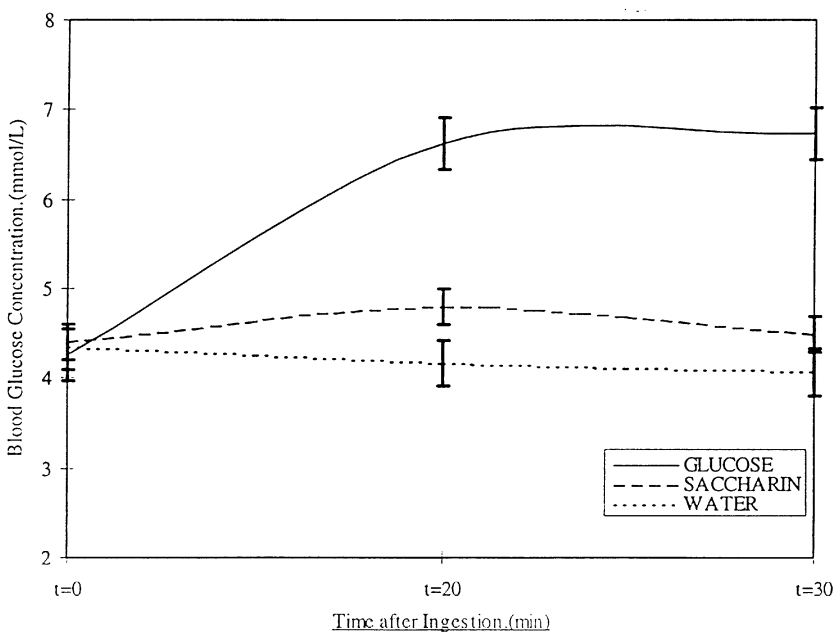

Fig. 3 Blood glucose profiles of the three treatment groups throughout the course of the experiment

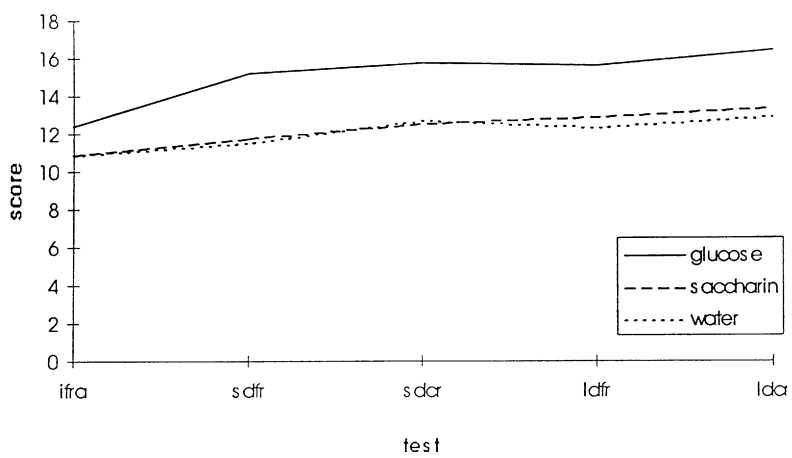

Fig. 4 Mean number of words recalled by each of the three treatment groups across the CVLT (list A only). The value shown for IFRa is the mean number of items recalled across the five trials

Table 1 Performance on different parameters of the CVLT in the three treatment groups

Treatment	FRa	IFRb	SDFR	SDCR	LDFR	LDCR	Recog	Discr	Bias	Persv	Intr
Gluc	62.1 (3.3)	10 (0.8)	15.2 (1.1)	15.8 (0.8)	15.6 (0.8)	16.4 (0.8)	18.8 (0.9)	96.0 (0.9)	−0.11 (0.1)	8.5 (2.1)	4.4 (1.1)
Sacch	54.5 (2.1)	9.3 (0.7)	11.8 (0.6)	12.6 (0.7)	12.9 (0.6)	13.4 (0.8)	17.7 (0.6)	94.6 (1.1)	−0.14) (0.1)	8.3 (1.0)	4.8 (1.9)
Water	54.4 (4.5)	9.5 (0.9)	11.5 (0.9)	12.7 (1.1)	12.3 (1.0)	12.9 (1.1)	18.6 (0.5)	91.9 (1.9)	−0.06 (0.1)	10.2 (2.7)	5.3 (1.5)

these tasks, the glucose group out-performed the two control groups, which each performed at comparable levels. There was no significant treatment effect on performance of the remainder of the tasks: IFRb, Digit Count (forwards or backwards) and the Rey-Osterrieth complex figure. There was, however, a trend on all these tests for the glucose-treated group to perform at the highest level overall. Where a significant treatment effect was observed (SDFR, SDCR, LDFR, LDCR), this effect did not interact significantly with delay.

When blood glucose level at t0 was treated as a covariate, all significant glucose effects which had been previously observed remained. This was also the case when immediate memory performance was used as a covariate.

Correlation analyses showed that delayed recall measures correlated with blood glucose concentration across all participants. This was the case even if immediate memory performance was partialled out.

California verbal learning test

Immediate free recall list A (IFRa)

A two-way ANOVA (treatment group, trials) revealed that the rate of list learning did not differ significantly across treatment groups [$F(8,108) = 1.20$, NS]. The number of words recalled on each progressive trial increased at a greater rate in the glucose treatment group, especially between trials 2 and 4, but not to a significant level.

Analysis of main effects showed that there was no significant treatment effect upon group performance on this task [$F(2,27) = 1.63$, NS]. As was expected, there was a highly significant main effect of trial on memory performance [$F(4,108 = 87.23$, $P < 0.0001$].

Immediate free recall list B (IFRb)

There were no significant differences in the performance of the three groups on this measure of performance [$F(2,27) = 0.20$, NS].

Short delay free recall (SDFR)

There was a significant treatment effect on the performance by the three groups on this trial [$F(2,27) = 5.29$, $P < 0.05$] (see Fig. 4 and Table 1). Further analysis revealed that there was no significant performance difference between the saccharin and water groups [$q(2,27) = 0.33$, NS], but that the glucose group performed significantly better than both the saccharin group [$q(2,27) = 3.80$, $P < 0.05$] and the water group [$q(3,27) = 4.14$, $P < 0.05$].

Short delay cued recall (SDCR)

There was a significant treatment effect on the performance of the three groups on this task [$F(2,27) = 4.21$, $P < 0.05$] (see Fig. 4 and Table 1). The post hoc analysis revealed no significant difference between the control groups [$q(2,27) = 0.11$, NS]. However, the performance of the glucose group was again significantly better than the water group [$q(2,27) = 3.50$, $P < 0.05$] and the saccharin group [$q(3,27) = 3.61$, $P < 0.05$].

Long delay free recall (LDFR)

There was a significant treatment effect on the performance of the three groups on this task [$F(2,27) = 4.18$, $P < 0.05$] (see Fig. 4 and Table 1). Post hoc analysis revealed no significant difference between the control groups [$q(2,27) = 0.69$, NS]. However, the performance of the glucose group was once more significantly better than that of the water treatment group [$q(3,27) = 3.84$, $P < 0.05$] and the saccharin group [$q(2,27) = 3.14$, $P < 0.05$].

SDFR and LDFR were separated by approximately 20 min. A two-way analysis of SDFR and LDFR performance revealed that there was no significant interaction between the treatment effect and delay [$F(2,27) = 0.51$, NS]. However, there was a significant main effect of delay on free recall performance [$F(1,27)= 7.34$, $P < 0.025$], indicating that a substantial degree of forgetting was occurring between the short and long test delay.

Long delay cued recall (LDCR)

There was a significant treatment effect on the performance on this task [$F(2,27) = 4.29$, $P < 0.05$] (see Fig. 4 and Table 1). Post hoc analysis revealed that there was no significant difference between the performance for the two control groups [$q(2,27) = 0.55$, NS]. The glucose-treated group again performed significantly better than the water group [$q(3,27) = 3.82$, $P < 0.05$] and the saccharin group [$q(2,27) = 3.28$, $P < 0.05$].

SDCR and LDCR were again separated by approximately 20 min. A two-way analysis of SDCR and LDCR performance revealed that there was no significant interaction between the treatment effect and delay [$F(2,27) = 0.67$, NS]. However, there was a significant main effect of delay on free recall performance [$F(1,27) = 6.13$, $P < 0.025$], again indicating that a substantial degree of forgetting was occurring between the short and long test delay.

Recall errors

There are two categories of recall error on the CVLT. These are perseverations (repetition of a word) and intrusions (recalling a word that was not amongst the test list). No significant treatment difference emerged in the number of perseverations [$F(2,27) = 0.26$, NS] or intrusions [$F(2,27) = 0.085$, NS].

Long delay recognition (LD recognition)

In terms of percentage correct recognition, there was no significant difference in group performance on this subtask of the CVLT [$F(2,27) = 1.36$, NS]. Furthermore, the use of signal detection parameters showed that there were no significant differences in the amount of discriminability shown by each group on this task [$F(2,27) = 2.36$, NS] or in their response bias [$F(2,27) = 0.10$, NS] (see Table 1).

Digit count

There was no significant difference on performance of this task when digits were presented either forwards [$F(2,27) = 0.13$, NS] or backwards [$F(2,27) = 1$, NS].

It is interesting to note that, whereas overall the three groups performed comparably, there was a relatively greater decline in the performance on the backwards task (compared with forwards performance) in the control groups. However, this difference in performance was not significant (see Table 2).

Table 2 Performance on digit span (forwards and backwards) and reproduction of the Rey-Osterrieth complex figure in the three treatment groups

Treatment	Digit span forwards	Digit span backwards	Rey-Osterrieth
Glucose	7.2 (0.7)	7.0 (0.8)	24.6 (1.8)
Saccharin	7.5 (0.7)	5.8 (0.5)	21.7 (1.7)
Water	7.7 (0.5)	6.5 (0.5)	20.1 (1.8)

Rey-Osterrieth complex figure

No significant differences in the scores of the 30-min reproduction of the figure emerged between the three treatment groups (see Table 2).

Covariate analyses

When performance on the delayed recall measures of the CVLT was covaried for initial blood glucose concentration at t0, the significant group differences which had been observed on SDFR, SDCR, LDFR and LDCR remained [$F(2,26) = 4.10$, $P < 0.05$; $F(2,26) = 4.16$, $P < 0.05$; $F(2,26) = 3.98$, $P < 0.05$ and $F(2,26) = 5.03$, $P < 0.05$, respectively].

Covarying for immediate free recall performance, the significant group differences which had been observed on SDFR, SDCR, LDFR and LDCR again remained [$F(2,26) = 5.23$, $P < 0.05$; $F(2,26) = 4.71$, $P < 0.05$; $F(2,26) = 3.90$, $P < 0.05$ and $F(2,26) = 3.80$, $P < 0.05$, respectively].

Correlations

Analysis of the Pearson's product moment correlation coefficient (one-tailed) across all participants (glucose, saccharin, water) showed that performance on short-delayed free and cued recall correlated significantly with blood glucose concentration at t20 ($r = 0.380$, $P < 0.05$; $r = 0.32$, $P < 0.05$, respectively). A significant correlation was also observed between blood glucose concentration at t40 and performance on free and cued recall performance after the long delay ($r = 0.38$, $P < 0.05$; $r = 0.43$, $P < 0.01$, respectively).

By contrast, performance on other memory measures did not correlate significantly with blood glucose concentration; for example, immediate memory performance did not correlate significantly with glucose concentration at t20 ($r = 0.16$, $P = 0.20$). This correlation was again computed for all participants.

When partial correlations were computed to control for differences in immediate memory performance across participants, all the correlations previously

reported between delayed recall and blood glucose concentration were preserved, with the exception of short delay cued recall, which approached significance (SDFR: $r = 0.3645$, $P < 0.05$; SDCR: $r = 0.2921$, $P = 0.06$; LDFR: $r = 0.39$, $P < 0.05$; LDCR: $r = 0.43$, $P < 0.01$].

Discussion

The findings of this study indicated that glucose can significantly improve memory functioning in normal young healthy participants. Physiologically, ingestion of glucose significantly elevated plasma glucose levels during the test period. By contrast, there was no significant rise in the blood glucose levels of either control group. Cognitively, glucose significantly enhanced the performance of participants on the delayed recall components of the CVLT. There were significant improvements in memory performance on short and long delay free recall tasks, and short and long delay cued recall tasks, and across all participants delayed recall performance correlated significantly with blood glucose concentration. The effects of glucose did not interact with test delay, indicating a more or less consistent effect between short and long delay verbal recall. Most significantly, these glucose facilitation effects were preserved when individual differences in resting blood glucose concentration and immediate memory recall were partialled out.

There were no significant treatment effects on the remainder of the tests of the CVLT. All groups performed comparably on the immediate free recall and long delay word recognition components of the CVLT and performance on these measures did not correlate with blood glucose concentration. In addition, there were no significant differences in the number or types of error made on any of the tasks by the three treatment groups. There were no significant differences in group performance on either the reproduction of the Rey-Osterrieth complex figure or on forwards/backwards digit recall. There was a trend for the glucose group to perform at a higher level than either control groups on all the tasks. However, this trend reached statistical significance on only the delayed recall tasks of the CVLT. The saccharin and water groups were not significantly different from each other on any of the memory tests given.

In this experiment, the influence of glucose administration on cognitive performance was investigated after overnight fasting. Therefore, it could be argued that rather than showing the beneficial influence of glucose, the results reflect the negative effect of fasting on memory performance. However, according to Marks and Rose (1981), hypoglycaemic symptoms start at blood glucose levels of approximately 2.2 mmol/l. In this experiment, all participants fell within the normal fasting range, but none reached levels that are associated with hypoglycaemia and its effect on memory performance. Moreover, no difference in performance levels could be seen in the immediate free recall and word recognition task of the CVLT, reproduction of the Rey-Osterrieth figure and digit recall, as might be expected if the findings merely reflected the negative effects of fasting.

Based upon the findings of this study, it may be inferred that glucose can significantly enhance memory in young participants on certain tasks. These findings are in contrast to those of Azari (1991), who found no evidence to support the hypothesis that glucose produces a dose-related enhancement of memory in young adults, or that a correlation exists between blood glucose response and memory performance. Note, however, that the doses of glucose used by Azari (30 g and 100 g) differed from that used in this investigation (25 g). Another explanation for the negative findings of Azari has already been proposed by Benton and Owens (1993). They suggested that the numbers of participants (18) used by Azari are statistically too few to reveal the sensitive memory enhancement afforded by glucose treatment. However, in the present study, it is noteworthy that the numbers of participants per treatment group was only ten.

To date, few studies have addressed directly the effect of glucose on human memory in young healthy adults. Research has centred on animal studies or investigation of effects on human participants in whom some form of memory impairment already exists. However, several researchers have concluded that increasing blood glucose levels may enhance some aspects of cognitive functioning in control participants. Benton (1989) proposed that increasing blood glucose levels improved controls' performance on undemanding mental tasks (cited by Benton 1990). Additionally, Benton et al. (1987) found that drinks containing glucose improved children's abilities to sustain attention. Benton and Sargent (1992) have argued that the time to search for and retrieve items from memory (a proposed reflection of levels of attention, alertness, and motivation) were associated with blood glucose concentration. Holmes et al. (1983) reported attentional deficits and slower performance of fine motor skills in individuals who were either hypo- or hyperglycaemic.

More closely related to the present study are the findings of Benton and Owens (1993), who, despite reporting no overall treatment effects, did note a significant correlation between blood glucose values and the number of words recalled in a short-term memory task. This effect was found irrespective of the initial blood glucose levels of participants and specifically did not relate to pre-test hypoglycaemic status. The observed correlation indicates a positive influence of glucose rather than merely the reversal of the negative effect of fasting. Lapp (1981) reported that lists of words were more easily learnt by participants with high

blood glucose measures (> 7.2 mmol/l) compared with those with low blood glucose levels (< 4.4 mmol/l) (cited by Benton and Owens 1993). As was observed in the present study, Benton and Owens (1993) found no association between blood glucose levels and performance on non-verbal recall tasks. Further reinforcing the findings of the present investigation are the results reported by Manning et al. (1992). In a similar study, Manning et al. reported that consumption of a glucose drink significantly improved memory for remembering a story and for word list recall. However, Manning et al. reported no effect on measures of digit span or visuospatial memory amongst the same participants. In the present study, given that performance on neither digit span nor reproduction of the Rey-Osterrieth figure lay close to ceiling levels, our data seem to indicate that the cognitive nature of the test may be the critical factor in determining whether a significant glucose facilitation effect is observed.

In summary, there is an emerging consensus from those studies which have demonstrated memory enhancement in young individuals that glucose specifically facilitates performance on word recall tasks, but has no significant benefit on measures of digit span or spatial memory. In contrast to the findings of Lee et al. (1988), who reported the existence of an inverse relationship between memory enhancement and treatment interval, no interaction between treatment × delay was observed in this study. This may be due to the relatively short duration of the test session, with completion of the trials within 45 min of glucose ingestion.

There are several aspects of the experimental design which should be discussed. Potentially the greatest weakness in this study was the adoption of a between-participant design. It may have been preferable to test participants on the three treatments and follow a within-participant analysis. Work is currently in progress in our laboratory which indeed adopts this approach. Nevertheless, effects observed in between-participant designs possibly indicate a more robust empirical phenomenon (see Gold 1992 for the case in support of between-participant glucose studies). Arguments that the group which received the glucose may have had intrinsically better memories are addressed by the following points: (i) participants were randomly allocated to different treatment groups; therefore it is unlikely that the glucose group would comprise individuals with significantly better memories, (ii) since treatments had been randomly allocated, it would not be expected that any variability between the participants within a group should be greater than the variability in participants within groups, (iii) all participants were university undergraduates; hence they had already been selected in having attained a high standard of educational performance (thus, general intellectual variability might be less than would be expected of a sample taken from the general population), (iv) the scores of the three groups were not significantly different on the Rey-Osterrieth test; the digit span and recall scores on immediate free recall of list B were almost identical (indeed, performance on all of the tests used was near identical when only the saccharin and water groups were compared) and (v) most powerfully, the significant differences and correlations which were observed with the delayed recall measures were preserved when individual differences in immediate memory were controlled for statistically.

Two further possible weaknesses in the experimental design are now considered. First, the reliance upon participants to fast overnight prior to testing. There was some variability in the resting blood glucose values shown across all the participants (3–5.4 mmol/l). However, whilst there were some individuals who fell below the normal fasting range (3.9–5.6 mmol/l), none of the participants exceeded this range at the start of the experiment. Whether fasting significantly alters the likelihood of a treatment effect to be observed is debatable: Benton and Owens (1993) reported that a significant effect of glucose emerged irrespective of the initial blood glucose levels. Second, although it was monitored closely, the accuracy with which participants performed the motor interference task (administered during the initial acquisition trials of the immediate free recall list A test of the cult) is another potential source of inter-participant variance in memory performance.

Another possibility which should be considered is that the glucose effect on memory may be mediated via enhanced arousal, alertness or motivation. As noted previously, the enhancement of memory following glucose administration appears to follow an inverted U-shaped dose-response function (Gold 1992). There is an interesting parallel in the arousal literature, in so far as an inverted U-shaped function has also been observed to describe the relationship between level of arousal and performance on certain tasks. This has been explained according to the Yerkes-Dodson Law (1908): performance efficiency is optimal at moderate levels of arousal, but declines at higher and lower levels of arousal (although the relationship between performance and arousal is modulated by other factors, such as task difficulty). It might therefore be the case that an optimal level of glucose produces an increased level of arousal compared with baseline levels, and this may mediate an enhanced level of memory (via a specific neurochemical and/or neurophysiological mechanism; see Gold and McGaugh 1975). However, an explanation of glucose facilitation in terms of arousal may well represent a significant oversimplification, as many other intervening factors are likely to be involved in mediating glucose's mechanism of action.

Memory studies in which glucose is administered prior to learning the test material do not permit a direct distinction to be made between the effects of glucose on memory retention and/or retrieval and its effects on

attention or on encoding of the material into long-term memory (Gold 1986). However, as glucose is known to facilitate memory performance when given both pre- and post-training, it has been argued that the facilitation effect cannot solely be the result of altered arousal or attention (Manning et al. 1992). Nevertheless, it remains possible that post-training administration of glucose could facilitate retention and/or retrieval of to-be-remembered material through increased arousal mechanisms. Ongoing research being conducted in our laboratory indicates that glucose facilitation of memory is not mediated via increased arousal, alertness or motivation. In the current study, having controlled statistically for individual differences in immediate memory performance, glucose-related facilitation of delayed recall was still present, indicating an effect via retention and/or retrieval mechanisms. Moreover, the fact that this glucose facilitation effect was present to a similar extent at both the short and long delay, and in both the cued recall and delayed recall data, indicates that the effect may have been mediated via enhanced storage of the associations involved in mediating the recall of information from long-term memory.

To summarize, it was found in this study that a dose of 25 g glucose can significantly enhance memory performance on a long-term verbal memory recall task in young healthy participants. This effect was maintained having controlled statistically for individuals' initial blood glucose levels and for their level of immediate memory performance. The mechanism of this effect seems to be via enhanced retention of associations in verbal long-term memory. Consistent with the findings of Benton and Owens (1993) and Manning et al. 1992), glucose treatment did not significantly alter participant performance on tests of spatial memory or digit recall. There was, however, a non-significant tendency for the glucose treated group to perform better on these tasks. It is possible that glucose does not enhance memory per se, but rather we acknowledge that it may have a more general effect upon cognition (Benton et al. 1994). This possibility is being explored further in our laboratory, although the data which we have obtained to date indicate that glucose does not exert its effect on memory through mechanisms such as non-specific alertness, arousal or motivation, or via selective attention.

Glucose has been reported to enhance several aspects of cognition, including recall (Manning et al. 1992; Benton and Owens 1993), improved attention (Holmes et al. 1983; Benton et al. 1994) and improved reaction time (Benton and Owens 1993; Holmes et al. 1983). In addition, the context in which glucose affects memory should be interpreted carefully, since high, low, rising and falling blood glucose levels have all been associated with improving memory (Benton et al. 1994). In future, these alternative possibilities should be considered more rigorously than has been the case in the literature to date. The brain regions through which the facilitation effect of glucose is mediated are also of interest. In future, non-invasive functional neuroimaging techniques may be able to inform our conception of the cognitive and physiological mechanisms involved by permitting us to visualize blood flow, brain metabolism and glucose utilization on-line, during the retrieval of different types of information in both healthy and memory impaired participants following glucose administration.

References

Azari NP (1991) Effects of glucose on memory processes in young adults. Psychopharmacology 105:521–524

Benton D (1989) Dietary sugar hyperactivity and cognitive functioning: a methodological review. J Appl Nutr 41:13–22

Benton D (1990) The impact of increasing blood glucose on psychological functioning. Biol Psychol 30:13–19

Benton D, Owens DS (1993) Blood glucose and human memory. Psychopharmacology 113:83–88

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

Cormier H, Winocur G, Craik F (1993) The effects of glucose on memory in young and elderly humans. Unpublished report, University of Toronto

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

Delis DC, Kramer JH, Kaplan E, Ober BA (1987) CVLT: Californian verbal learning test. The Psychological Corporation/Harcourt Brace Jovanovich, New York

Drachman DA, Leavitt J (1974) Human memory and the cholinergic system. Arch Neurol 30:113–121

Fibiger HC (1991) Cholinergic mechanisms in learning, memory and dementia: a review of recent evidence. Trends Neurosci 14:220–223

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: Frederickson RCA, McGaugh JL, Felten DL (eds) Peripheral signaling of the brain: role in neural-immune interactions and learning and memory. Hogrefe and Huber,Toronto, pp 391–419

Gold PE (1992) Modulation of memory processing: enhancement of memory in rodents and humans. In: Squire LR, Butters N (eds) The neuropsychology of memory, 2nd edn. Guilford Press, New York, pp 402–414

Gold PE, McGaugh JL (1975) A single-trace, two-process view of memory storage processes. In: Deutsch D, Deutsch AJ (eds) Short term memory. Academic Press, New York, pp 355–390

Gradman TJ, Laws A, Thompson LW, Raven GM (1993) Verbal learning and/or memory improves with glycemic control in older participants with non-insulin-dependent diabetes mellitus. J Am Geriatr Soc 41:1305–1312

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

Hasselmo ME, Bower JM (1993) Acetylcholine and memory. Trends Neurosci 16:218–222

Holmes CS, Hayford JT, Gonzalez JL, Weydert JA (1983) A survey of cognitive functioning at different glucose levels in diabetic persons. Diabetes Care 6:180–185

Lapp JE (1981) Effects of glycemic alterations and noun imagery on the learning of paired associates. J Learn Disord 14:35–38
Lee MK, Graham SN, Gold PE (1988) Memory enhancement with posttraining intraventricular glucose injections in rats. Behav Neurosci 102:591–595
Manning CA, Parsons MW, Gold PE (1992) Anterograde and retrograde enhancement of 24-h memory by glucose in elderly humans. Behav Neural Biol 58:125–130
Manning CA, Ragozzino ME, Gold PE (1993) Glucose enhancement of memory in patients with probable senile dementia of the Alzheimer's type. Neurobiol Aging 14:523–528
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 sec blood glucose meter. Lancet 1:778–779
Meneilly GS, Cheung E, Tessier D, Yakura C, Tuokko H. (1993) The effect of improved glycemic control on cognitive functions in the elderly patient with diabetes. J Gerontol 48:M117–M121
Messier C, Gagnon M (1996) Glucose regulation and cognitive functions: relation to Alzheimer's disease and diabetes. Behav Brain Res 75:1–11
Osterrieth PA (1944) Le test de copie d'une figure complexe. Arch Psychol 30:206–356
Parsons MW, Gold PE (1992) Glucose enhancement of memory in elderly humans: an inverted-U dose response curve. Neurobiol Aging 13:401–404
Perlmutter LC, Hakami MK, Hodgson-Harrington C, Ginsberg J, Katz J, Singer DE, Nathan DM (1984) Decreased cognitive function in aging non-insulin dependent diabetic patients. Am J Med 77:1043–1048
Ryan CM, Williams TM (1993) Effects of insulin-dependent diabetes on learning and memory efficiency in adults. J Clin Exp Neuropsychol 15:685–700
Sieber FE, Traystman RJ (1992) Special issues: glucose and the brain. Crit Care Med 20:104–114
Stone WS, Wenk GL, Olton DS, Gold PE (1990) Poor blood glucose predicts sleep and memory deficits in normal aged rats. J Gerontol 45:169–173
Wechsler DA (1981) Wechsler adult intelligence scale – revised. Manual. Psychological Corporation, New York
Wechsler DA (1987) Wechsler memory scale – revised. Harcourt Brace Jovanovich, New York
Wenk GL (1989) An hypothesis on the role of glucose in the mechanism of action of cognitive enhancers. Psychopharmacology 99:431–438
White NM (1991) Peripheral and central memory enhancing actions of glucose. In: Frederickson RCA, McGaugh JL, Felten DL (eds) Peripheral signaling of the brain: role in neural-immune interactions and learning and memory. Hogrefe and Huber, Toronto, pp 421–441
Winocur G (1995) Glucose-enhanced performance by aged rats on a test of conditional discrimination-learning. Psychobiology 23:270–276
Yerkes RM, Dodson JD (1908) The relation of strength of stimulus to rapidity of habit formation. J Comp Neurol Psychol 18:459–482