

# Cognitive performance is associated with glucose regulation in healthy elderly persons and can be enhanced with glucose and dietary carbohydrates<sup>1-3</sup>

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## ABSTRACT

**Background:** A glucose drink has been shown to improve memory in persons with poor glucose regulation and poor cognition.

**Objective:** The objective of this study was to determine 1) whether an association between cognition and glucose regulation is apparent in healthy seniors and 2) the effects of dietary carbohydrates on cognition.

**Design:** After an overnight fast, 10 men and 10 women (aged 60–82 y) consumed 50 g carbohydrate as glucose, potatoes, or barley or a placebo on 4 separate mornings. Cognitive tests were administered 15, 60, and 105 min after ingestion of the carbohydrate. Plasma glucose and serum insulin were measured.

**Results:** In a multiple regression analysis, poor baseline (placebo) verbal declarative memory (immediate and 20-min delayed paragraph recall and word list recall) and visuomotor task performance were predicted by poor  $\beta$  cell function, high incremental area under the glucose curve, low insulin resistance, and low body mass index. The difference in plasma glucose after food consumption [glucose > potatoes > barley > placebo ( $P < 0.03$ )] did not predict performance. Although overall performance did not differ with consumption of the different test foods, baseline score and  $\beta$  cell function correlated with improvements in immediate and delayed paragraph recall for all 3 carbohydrates (compared with placebo); the poorer the baseline memory or  $\beta$  cell function, the greater the improvement (correlation between  $\beta$  cell function and improvement in delayed paragraph recall:  $r > -0.50$ ,  $P < 0.03$ ). Poor  $\beta$  cell function correlated with improvement for all carbohydrates in visuomotor task performance but not on an attention task.

**Conclusions:** Glucose regulation was associated with cognitive performance in elderly subjects with normal glucose tolerance. Dietary carbohydrates (potatoes and barley) enhanced cognition in subjects with poor memories or  $\beta$  cell function independently of plasma glucose. *Am J Clin Nutr* 2000;72:825–36.

**KEY WORDS** Glucose, carbohydrates, insulin, memory, cognition, elderly subjects,  $\beta$  cells, insulin resistance, glucose regulation, glucose tolerance

## INTRODUCTION

The proportion of North Americans with cognitive impairments is increasing as the population ages. It is important to

understand environmental factors, such as nutrition, that may help prevent or reduce such deficits (1). However, research examining the role of specific macronutrients on cognitive function in adults is inconclusive (2, 3).

Several lines of evidence suggest that impaired glucose regulation is associated with impaired cognition and that improved regulation leads to cognitive improvements. Elderly subjects with type 2 diabetes generally perform worse on memory tests than do age-matched control subjects (4), and nondiabetic subjects with poor glucose regulation perform worse than do those with better regulation (5–12). Moreover, diabetes-associated cognitive deficits can be enhanced by improving glucose regulation with oral hypoglycemic agents (13, 14).

A wide range of studies have shown that a glucose drink enhances cognitive performance compared with a placebo drink in healthy subjects and in subjects with memory deficits or poor glucose regulation (15). Performance is improved more consistently in healthy elderly subjects (7, 16) and in patients with Alzheimer disease (10, 17, 18), who usually have poor memories and glucose regulation (19), than in healthy young subjects. Generally, testing begins 15–20 min after ingestion of the glucose (usually 50 g), and it has been suggested that a specific

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range of blood glucose concentration (8–10 mmol/L) is optimal for improved memory (17, 20, 21). The benefits appear to be most robust on tests of declarative long-term verbal memory (conscious recollections about facts or events) (8, 16, 22, 23), which is mediated by the medial temporal lobe, including the hippocampus and related structures (24).

In contrast with the glucose-drink studies, research on the effect of meals on cognitive function in healthy adults has yielded few conclusions about the effects of specific macronutrients on performance (2, 3). The lack of consistent findings may be because these studies used very different paradigms, with testing usually beginning 30 min to 4 h after meal ingestion; additionally, only young adults were investigated.

Although the influence of glucose drinks on memory has been examined extensively, the influence of raising blood glucose concentration with common carbohydrate foods on cognitive performance has not been tested systematically. Thus, it is not known whether glucose has a special effect on cognitive function or whether any carbohydrate or energy source has a similar effect.

The purpose of the present study was to determine whether measures of glucose regulation were associated with cognition in healthy elderly persons with normal fasting plasma glucose [ $<6.1$  mmol/L (25)] and to determine the influence of glucose and common carbohydrate foods on memory and nonmemory cognitive performance in these subjects. The importance of the time point after ingestion on performance was also examined.

## SUBJECTS AND METHODS

### Subjects

Ten male and 10 female free-living subjects aged 60–82 y were contacted through a database of previously recruited subjects at the Memory Laboratory of the University of Toronto. Subjects participated voluntarily; compensation was provided for travel. All procedures were approved by the Baycrest Centre for Geriatric Care and the University of Toronto ethics committees. Only subjects who spoke English as their native language were selected. Level of education ranged from 8 to 12 y. Evidence of diabetes [fasting plasma glucose  $\geq 7.0$  mmol/L (25)] or cognitive decline [below age- and education-adjusted lower quartile on the Mini-Mental State Examination (MMSE; 26, 27)] were used as exclusion criteria. However, all subjects recruited met these criteria; no subjects were excluded.

### Procedure

A repeated-measures crossover design was used such that each subject served as his or her own control and participated in all of the 4 sessions. After an overnight (10–12 h) fast during which only water was permitted, the subjects arrived at the testing center at 0830 on the first day to complete a 30-min screening and at 0900 on the remaining 3 d. Each subject was tested individually with one test food or drink on 4 separate mornings, each separated by  $\approx 1$  wk and  $\geq 2$  d to minimize potential carryover effects. The 4 test foods and drinks were placebo or 1 of 3 treatments containing 50 g of available carbohydrate (carbohydrate minus dietary fiber): a glucose drink, instant mashed potatoes, or barley. The subjects were blinded to the placebo and glucose treatments. The order of the 4 sessions was counterbalanced such that each treatment was tested equally often on each day.

The glucose and placebo drinks were tested in an attempt to repeat the previously reported findings that 50 g glucose enhances declarative memory relative to placebo in healthy elderly subjects (8, 10, 16, 20, 23, 28, 29). Mashed potatoes [high glycemic index (GI)] and barley (low GI) also containing 50 g carbohydrate were used to specifically test high-carbohydrate foods with very different effects on blood glucose (30).

The format for each of the 4 sessions was identical except for the first session, in which subject screening took place before testing. During screening, the subjects were administered the MMSE, fasting plasma glucose was measured for evidence of diabetes, and height and weight were measured. The subjects were also administered sample versions of each cognitive test to decrease the risk of practice effects once the subjects had experience with the test.

At 0900, blood was collected by finger prick and analyzed for fasting serum insulin at a later date. One additional drop was collected for measurement of fasting plasma glucose. After blood collection, the test food or drink was given to the subject, who was asked to try to consume the entire amount within  $\approx 5$  min (drinks) or 10 min (foods). Plasma glucose was measured for each subject at 15, 60, and 105 min after the start of consumption of the test food or drink. Immediately after blood collection at 15 min, the subjects were tested on 3 verbal memory tasks (immediate word list recall and immediate and 20-min delayed paragraph recall). These memory tests were used because in previous studies glucose was shown to consistently enhance performance on similar tests in healthy elderly subjects (8, 16, 20, 23, 28, 29). The subjects were first tested on immediate recall of an audiotaped narrative word list. Immediately after this test, immediate recall of an audiotaped narrative paragraph was tested. After a 20-min delay during which they were distracted with nonverbal tasks, the subjects were tested for recall of the same paragraph. The delay period was filled with a version of a visuomotor task [Trail Making Test (or Trails) Part B Adult Form (31)], which is known to test general brain functions, and an attention task requiring the subjects to attend to specific aspects of a television program.

After blood collection at 60 min, the subjects were tested with alternative versions of the same tests. Thus, each subject was tested on all 3 declarative memory tasks, Trails, and the attention task both 15 min and 60 min after consumption of the test food or drink. At 105 min, the subjects were given the immediate word list recall test and Trails only (no paragraph recall or attention task). Eight different versions of the paragraph recall and attention tests and 12 versions of the word list and Trails tests were required. The order of administration of the 8 different versions of each test was counterbalanced across the 15- and 60-min time points such that each test version was paired equally often with each food or drink. The 4 additional versions of the word list test and Trails were counterbalanced with test food or drink at the 105-min time point only.

### Dietary treatments

The 4 dietary treatments were 1) placebo: 300 mL lemon beverage (290 mL water and 10 mL lemon juice) sweetened with 23.7 mg sodium saccharin (Hermesetas Original; JL Freeman Inc, Boucherville, Canada), 2) glucose: 300 mL lemon beverage (290 mL water and 10 mL lemon juice) containing 50 g glucose (Dextrose monohydrate; Bio-Health, Dawson Traders Ltd, Toronto), 3) potato: 50 g of available carbohydrate from instant



mashed potatoes (Carnation Mashed potatoes; Carnation Foods Company Ltd, Carberry, Canada), and 4) barley: 50 g of available carbohydrate from pearly barley (McNair pearl barley; McNair Products Co Ltd, Montreal). The placebo and glucose drinks were matched for sweetness in order to blind subjects to the treatment (16). The instant mashed potatoes were prepared by using the package directions, but instead of adding water, milk, butter or margarine, and salt, only water was added (equivalent to recommended amount of water plus milk); 61 g potato flakes was added to 240 mL water and heated at full power in a microwave oven for 1.5 min. Barley was prepared by adding 60 g barley to 420 mL boiling water; the barley was cooked until all of the water was absorbed ( $\approx 30$  min).

The subjects were given 2.5 g butter (Gay Lea unsalted; Gay Lea Foods, Weston, Canada) and salt and pepper as desired, and 120 mL water (President's Choice Natural Spring Water; Sun-fresh Ltd, Toronto) to drink with the barley and potatoes to improve palatability and compliance. The weight (in g), volume (in mL), protein (in g), carbohydrate (in g), fat (in g), energy [in kJ; based on previous analysis (32)], and GI values [white bread = 100 (33)] for the 4 dietary treatments were as follows: placebo (300, 300, 0, 0, 0, 0, and 0), glucose (300, 300, 0, 50, 837, and 142), potato (312, 325, 4, 50, 2, 979, and 118), and barley (196, 200, 5, 50, 2, 996, and 36).

## Cognitive tests

### Memory tests

Word list recall is a test of short-term verbal declarative memory that is demonstrated by the recall of material immediately after it is presented and is of limited capacity; the information can be held for up to several minutes but will be lost or replaced by new information unless it is sustained by rehearsal (34). A variation of the Rey Auditory-Verbal Learning Test (27) was developed. Twelve different word lists were constructed to be similar in difficulty. Twelve unrelated, but familiar, 2-syllable nouns made up each list. Word frequency (35) was similar in each version to make the lists of similar difficulty. Each word list was recorded on audiotape; words were spoken at a rate of  $\approx 1/s$ . The subjects listened to the same list 3 times in succession and were asked to immediately recall as many words as possible (including words already repeated), in any order, after each administration. Recalls were tape recorded to improve scoring accuracy. The number of words recalled was scored for each of the 3 administrations. Differences from the first to the second to the third presentations of the list represent learning (27).

For paragraph recall, immediate and delayed (20 min) recall were examined to differentiate between short (immediate) and long-term (delayed) memory functions. A total score (immediate + delayed) was also used to assess overall paragraph recall performance. Long-term memory can be defined as the "ability to recall information after an interval during which attention is focused away from the target information" (34). Eight paragraphs of comparable difficulty, length, and context, similar to the Logical Memory subtest of the Wechsler Memory Scale—Revised [WMS-R (36)], were used. Each paragraph contained 25 ideas or scoring units. The 2 original paragraphs from the WMS-R, 1 paragraph from the new WMS-III (37), and 3 additional paragraphs (Morris revision) that were developed to be similar to these 3 paragraphs (38), were used. Finally, we developed 2 paragraphs (Kaplan revision) to be similar to the 2 original WMS-R paragraphs. These paragraphs were developed on the basis of

Morris' criteria (38) to be similar in number of sentences, words per sentence, total words, total syllables, syllables per sentence, syllables per word, and textual readability [evaluated by the Flesch-Kincaid Index, the Flesch Index, and the Fog Index (39)]. Specific scoring criteria were used for each paragraph.

For each test, the subjects listened to one paragraph on audiotape. Immediately after hearing the paragraph, the subjects were asked to recall as much of the story as they could in words that were as close as possible to the original words (short-term memory). After a 20-min delay period, the subjects were again asked to recall as much as they could from the paragraph (long-term memory). The subjects' answers were recorded on audiotape to improve scoring accuracy. The subjects were distracted with nonverbal stimuli (visuomotor and attention tasks) during the delay period to discourage them from rehearsing.

### Visuomotor test

Twelve alternative versions of the standard Trails Part B Adult Form (31) were used (original plus 11 new versions). This test measures speed for visual search, attention, mental flexibility, and motor function (27) and is a sound measure of general brain functions. Subjects are required to connect 25 encircled numbers and letters, somewhat randomly arranged on a page, in proper order (1 then A, then 2 then B, and so on) as quickly as they can. Time to complete the test was used as a measure of performance (shorter times represent better scores). The subjects were corrected by the experimenter when mistakes were made, but the timer was not stopped during this time.

### Attention test

The principal purpose of the attention test was to provide subjects with distracting stimuli during the delay period after immediate paragraph recall such that subjects would have difficulty rehearsing. However, this task was also used as an attention task. The subjects watched 1 of 4 episodes of a popular situation comedy on videotape. A different episode was viewed during each of the 4 sessions. The subjects watched the first 10 min of each episode during the first delay period and the last 10 min during the second delay period. While watching the television program, the subjects were asked to keep track (by marking on a page) of the number of times each of the main characters' names or specific words were spoken and the number of times doors opened and closed. The percentage correct over the entire 20-min episode was used as the score on this task.

## Blood glucose and insulin analyses

Blood was collected by finger prick into an empty vial (Eppendorf Scientific, Inc, Westbury, NJ) with a Penlet II Automatic Blood Sampler lancet device (Lifescan Canada Ltd, Mississauga, Canada). One drop of blood was used to measure plasma glucose with use of a blood glucose meter (One Touch Basic Meter; Lifescan Canada Ltd). This meter has been reported to be accurate to within 15% of laboratory results 96% of the time (One Touch Basic Test Strip package insert, 1997).

Approximately 5 drops of fasting blood were collected into an empty 1.5-mL vial (Eppendorf Scientific Inc) for serum insulin analysis. The blood was left at room temperature to clot. After each session, the vials were spun on a Beckman Microfuge II (Beckman Instruments Inc, Brea, CA) at  $9000 \times g$  for 10 min at room temperature and the serum was removed and frozen at  $-70^\circ\text{C}$  until analyzed. Samples were analyzed in duplicate at the Bant-

**TABLE 1**  
Characteristics of the subjects<sup>1</sup>

	All subjects (n = 20)	Men (n = 10)	Women (n = 10)
Age (y)	72.3 ± 1.4	74.8 ± 1.9	69.7 ± 1.9
Education (grade)	10.6 ± 0.3	10.1 ± 0.5	11.0 ± 0.4
MMSE (out of 30)	28.0 ± 0.3	27.6 ± 0.5	28.4 ± 0.3
BMI (kg/m <sup>2</sup> )	25.1 ± 0.9	25.7 ± 1.3	24.6 ± 1.4
Fasting plasma glucose (mmol/L)	5.4 ± 0.1	5.4 ± 0.2	5.4 ± 0.1
Fasting serum insulin (pmol/L)	52.5 ± 5.6	55.2 ± 7.6	49.8 ± 8.7
β Cell function (%) <sup>2</sup>	78.4 ± 7.1	79.8 ± 7.9	77.0 ± 12.1
Insulin resistance <sup>2</sup>	1.77 ± 0.22	1.90 ± 0.31	1.65 ± 0.30
gAUC <sup>3</sup>	325.1 ± 35.3	333.2 ± 42.3	316.9 ± 56.2

<sup>1</sup> $\bar{x} \pm \text{SEM}$ . MMSE, Mini-Mental State Examination; gAUC, incremental area under the glucose response curve. There were no significant differences between men and women.

<sup>2</sup>Calculated from fasting plasma glucose and insulin concentrations by using Homeostasis Model Assessment (40).

<sup>3</sup>Determined from plasma glucose concentrations 0, 15, 60, and 105 min after ingestion of a 50-g glucose drink.

ing and Best Diabetes Core Laboratory, University of Toronto, by using radioimmunoassay (Pharmacia Insulin RIA, Dorval, Canada). At the time of analysis, serum samples from all 4 sessions for each subject were pooled to get one estimate of fasting serum insulin for each subject. The main reason for using this method of collection was to improve compliance. The insulin assay required  $\approx 250 \mu\text{L}$  serum for accurate duplicate analysis. We believed that using an additional, more invasive blood collection technique (ie, collection of venous blood) may have deterred subjects from participating.

Homeostasis model assessment (HOMA) was used to estimate β cell function and insulin resistance from fasting plasma glucose (average of all 4 sessions) and insulin concentrations (40). This model was highly correlated with estimates from other standard techniques (40). One-hundred-percent β cell function and an insulin resistance value of 1.00 represent normal values for a normal-weight healthy person aged  $\leq 35$  y; lower β cell and higher insulin resistance values represent relative impairments. Incremental area under the glucose response curve (gAUC) was determined from the plasma glucose values obtained after the consumption of the glucose drink.

### Statistical analyses

Statistical analyses were conducted by using SAS 6.12 (SAS Institute Inc, Cary, NC). Repeated-measures analysis of variance (ANOVA) was used to determine the influence of food, time, delay (paragraph recall), repeat (3 presentations of word lists), and sex and their interactions on performance for each test. Simple contrasts were used to determine the effect of each food or drink compared with placebo. Contrasts comparing successive means were used for predicted outcomes (food effects on plasma glucose and Trails performance over time). To assess the relation between baseline cognitive performance and glucose regulation, linear and multiple regression analyses were conducted using performance under the placebo condition as the response variable and β cell function, insulin resistance, gAUC (41), and body mass index (BMI; in  $\text{kg}/\text{m}^2$ ) as predictor variables. To assess the effect of each carbohydrate on cognitive performance, linear and multiple regression analyses were conducted using performance for each dietary treatment compared with placebo (improvement

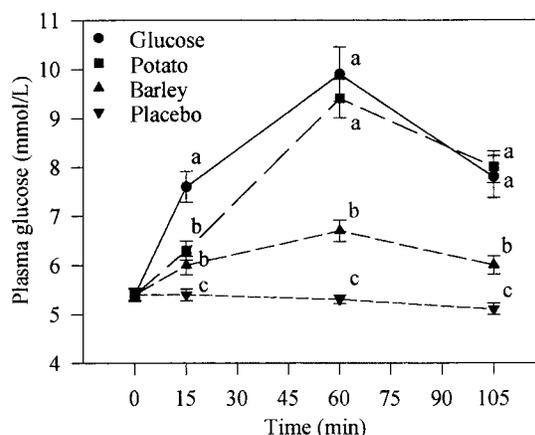
with food) as the response variable and overall placebo score (baseline performance), β cell function, insulin resistance, and gAUC as predictor variables. Because of the potential for multicollinearity among response variables, the best model was predicted by determining the subset of response variables that had the highest adjusted  $R^2$  value (42). An analysis of the risk of regression to the mean (43) was conducted to determine the appropriateness of regressing baseline performance against the improvement with food. A multivariate ANOVA to test for homogeneity of slopes among dietary treatments was conducted. Statistical significance was set at  $P < 0.05$ . Results are reported as means  $\pm$  SEMs unless indicated otherwise.

## RESULTS

### Characteristics of food ingestion and effects on glucose regulation

All 20 subjects consumed the placebo and glucose drinks within 6 min (placebo,  $2.5 \pm 0.3$  min; glucose,  $2.7 \pm 0.3$  min) and the potatoes and barley within 16 min (potatoes,  $9.4 \pm 0.7$  min; barley,  $10.7 \pm 0.7$  min). The placebo and glucose drinks were entirely consumed by all subjects; 4 subjects did not consume all of the potatoes and 5 subjects did not consume all of the barley. Consumption of potatoes and barley was  $95.2 \pm 2.3\%$  and  $91.3 \pm 4.2\%$ , respectively. On a palatability scale of 0 (very pleasant) to 10 (not at all pleasant), the glucose drink was rated by the subjects as most palatable ( $2.6 \pm 0.5$ ), followed by placebo ( $4.1 \pm 0.6$ ;  $P = 0.0004$ ), then potato ( $6.1 \pm 0.6$ ;  $P = 0.0245$ ), which did not differ significantly from barley ( $6.6 \pm 0.6$ ). Subject characteristics and glucose regulation measurements are reported in **Table 1**. No significant differences in any of these measures were evident between men and women.

The influences of the 4 dietary treatments on plasma glucose at each time point are shown in **Figure 1**. As expected, glucose-drink and potato consumption caused the largest rise in plasma glucose concentration, followed by barley and then the placebo drink. Significant differences in incremental area under the glucose response curve were observed among all 4 groups. Mean incremental area under the curve after glucose ingestion



**FIGURE 1.** Mean  $\pm$  SEM plasma glucose response to test foods and drinks after initial consumption. Values with different letters at each time point are significantly different: 15 min,  $P < 0.0016$ ; 60 and 105 min,  $P < 0.0001$ .

**TABLE 2**  
Linear and multiple regressions between cognitive performance and glucose regulation<sup>1</sup>

	gAUC		β Cell function		Insulin resistance		BMI		Multiple regression <sup>2</sup>		
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	Significant predictors	<i>R</i> <sup>2</sup>	<i>P</i>
Paragraph											
Imm	-0.42	0.0712	0.33	NS	0.42	0.0737	0.48	0.0355 <sup>3</sup>	gAUC, BMI	0.39	0.0196 <sup>3</sup>
Del	-0.41	0.0781	0.30	NS	0.51	0.0244 <sup>3</sup>	0.48	0.0377 <sup>3</sup>	gAUC, BC, IR, BMI	0.47	0.0506
Total	-0.43	0.0688	0.32	NS	0.48	0.0398 <sup>3</sup>	0.49	0.0327 <sup>3</sup>	gAUC, BMI	0.40	0.0174 <sup>3</sup>
Word list <sup>4</sup>											
1	-0.47	0.0431 <sup>3</sup>	0.17	NS	0.25	NS	0.45	0.0534	gAUC, BMI, BC	0.44	0.0292 <sup>3</sup>
2	-0.31	NS	0.01	NS	0.13	NS	0.23	NS	None	—	—
3	-0.36	NS	0.01	NS	-0.04	NS	0.20	NS	None	—	—
Total	-0.39	0.0948	0.06	NS	0.10	NS	0.29	NS	None	—	—
Trails <sup>5</sup>											
Total	0.47	0.0405 <sup>3</sup>	-0.21	NS	-0.40	0.0918	-0.23	NS	gAUC, IR, BC	0.38	0.0579
Attention											
Total	-0.14	NS	-0.25	NS	-0.16	NS	0.15	NS	None	—	—

<sup>1</sup>gAUC, incremental area under the glucose response curve; imm, immediate recall over both time points (15 and 60 min) combined; del, delayed recall over both time points combined; NS, not significant. β cell function (BC) and insulin resistance (IR) were calculated from fasting plasma glucose and insulin concentrations by using Homeostasis Model Assessment (40).

<sup>2</sup>Multiple regression analysis (cognitive performance on each test used as response variable and gAUC, BC, IR, and BMI used as predictor variables). The subset of variables with the highest adjusted *R*<sup>2</sup> are given (actual *R*<sup>2</sup> shown in table). Predictors had to meet the 0.1500 significance level for entry into the model.

<sup>3</sup>*P* ≤ 0.05.

<sup>4</sup>1, 2, and 3 represent scores on the first, second, and third presentations of work lists over all 3 time points (15, 60, and 105 min) combined; total refers to the score over all time points combined.

<sup>5</sup>A lower score (faster) represents better performance.

(325.1 ± 34.3) > potato (269.6 ± 21.4; *P* = 0.033) > barley (85.3 ± 10.9; *P* < 0.0001) > placebo (-11.1 ± 7.1; *P* < 0.0001).

### Relation between baseline cognitive performance and glucose regulation

The relation between baseline cognitive performance (performance during the placebo condition) and measures of glucose regulation in subjects with normal fasting plasma glucose (<6.1 mmol/L) was determined by linear and multiple regression analysis. This analysis included data for 19 of the 20 subjects; one male subject who had impaired fasting glucose (mean of 4 samples: 6.4 mmol/L) was excluded.

Total scores (combining scores at all time points) on each test were used as the response variables for this analysis because only performance with placebo was examined; there was no need to assess a time effect. β Cell function and insulin resistance (assessed from fasting glucose and insulin), gAUC (determined from the blood glucose response to the glucose drink), and body mass index (BMI; in kg/m<sup>2</sup>) were used as the predictor variables. The linear regression analyses for each cognitive test are presented in **Table 2**, and the linear regressions between total paragraph recall performance (an overall paragraph recall score) and measures of glucose regulation and BMI are shown in **Figure 2**. Collectively, these data suggest an association among poor cognitive performance and high gAUC, low insulin resistance (good insulin sensitivity), and low BMI. There was a trend for poorer performance to be associated with poor (low) β cell function, but no significant associations were observed. No systematic differences were observed between men and women.

It is important to note the regressions among the predictor variables. BMI was significantly associated with β cell function (*r* = 0.58, *P* = 0.0100) and insulin resistance (*r* = 0.70, *P* = 0.0008). β Cell function was significantly associated with insulin resistance (*r* = 0.79, *P* < 0.0001). In contrast, gAUC was

not associated with any of the other variables. These results indicate that the significant influences of insulin resistance and BMI on cognitive function may be strongly related to each other.

The results of the multiple regression analyses are also shown in **Table 2**. These results indicate that the predictors were able to account for between 38% and 47% of the variation in paragraph recall, word list recall (first presentation only), and Trails performance. An important observation from the multiple regression analyses was that β cell function, which did not significantly predict performance in the linear regression analyses, was a significant predictor of cognitive performance.

Overall, the linear and multiple regression analyses generally suggested that subjects with relatively high gAUC, poor β cell function, good insulin sensitivity, and low BMI performed worse on several cognitive tests. The opposite profile of glucose regulation and BMI suggested superior performance.

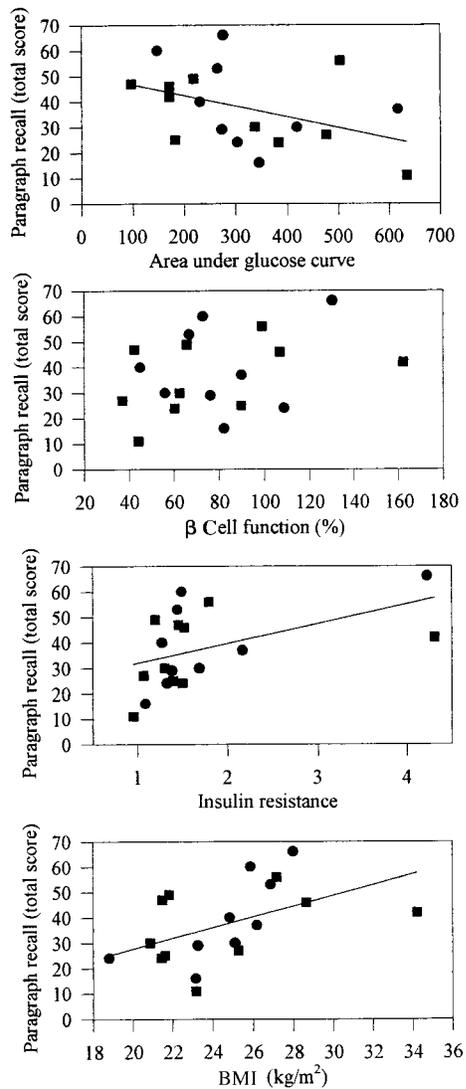
### Effects of glucose and dietary carbohydrates on cognitive performance

When the effects of food consumption on performance were examined, data for all 20 subjects were included. Overall performance after consumption of glucose, potatoes, or barley did not significantly differ from performance after placebo ingestion on any of the cognitive tests (data not shown).

#### Paragraph recall

In contrast, when baseline performance and measures of glucose regulation were factored into the analyses, both poor baseline memory and poor β cell function were associated with improvements in memory performance for all 3 carbohydrates (glucose, potato, and barley) compared with placebo.

The mean score on immediate paragraph recall for all subjects was 10.3 ± 0.3 and the top score was 20 (out of 25). Thus, no subject reached ceiling performance.



**FIGURE 2.** Linear regression analyses for regression between paragraph recall performance (total score on all 4 tests: immediate and delayed recall at 15 and 60 min combined) and measures of glucose regulation and body mass index for all 19 subjects. Regression lines shown if  $P < 0.10$ . Data for men (●) and women (■) are shown for comparison.  $r$  and  $P$  values for all subjects were as follows: area under glucose curve,  $r = -0.43$ ,  $P = 0.0688$ ;  $\beta$  cell function,  $r = 0.33$ ,  $P = 0.1786$ ; insulin resistance,  $r = 0.48$ ,  $P = 0.0398$ ; and BMI,  $r = 0.49$ ,  $P = 0.0327$ . Note that the  $r$  value for insulin resistance changed only slightly (to 0.44) when the 2 subjects with the highest insulin resistance were removed.

Repeated-measures ANOVA for paragraph recall showed an effect of delay ( $P < 0.0001$ ), as anticipated; performance was better for immediate than for delayed recall. No main effect of food (glucose, potato, or barley), time (15 compared with 60 min), or sex on performance was observed. However, a food  $\times$  delay interaction ( $P = 0.0357$ ) was apparent, suggesting that the effect of food consumption was dependent on the test (immediate or delay) examined.

Because the results of previous studies suggest that individuals with poor memories and poor glucose regulation may be more sensitive to the cognitive-enhancing effects of glucose than are other individuals, linear and multiple regression analy-

ses were performed using improvement with each food (food score – placebo score) as the response variable and baseline score (combined placebo score on all 4 paragraph recall tests: immediate and delayed recall at 15 min and at 60 min), and measures of glucose regulation ( $\beta$  cell function, insulin resistance, and gAUC) as predictor variables. The risk of observing regression to the mean by comparing baseline score with improvement with food was determined to be minimal because baseline scores were highly correlated with total paragraph recall scores with each of the other dietary treatments ( $r > 0.65$ ,  $P < 0.002$  for all 3 carbohydrates).

Baseline performance and glucose regulation measurements were associated with improvements in performance for all 3 carbohydrates.  $\beta$  Cell function was a better predictor of improvement than was insulin resistance or gAUC. Linear correlations between improvement and baseline score and between improvement and  $\beta$  cell function are shown in **Table 3**. Data are presented separately for the immediate and delayed recall scores at the 15- and 60-min time points and for total scores at each time point and total immediate and total delayed recall scores. There were no significant correlations between improvement and insulin resistance, and only improvement with barley at 15 min delayed recall and 15 min total recall were significantly correlated with gAUC ( $P < 0.04$ ). The results of multiple regression analyses are also shown and suggest that relatively poor  $\beta$  cell function, poor baseline performance, and good insulin sensitivity were all associated with various measures of improvement. These results show that the associations were generally stronger on tests of delayed recall (long-term memory) than on tests of immediate recall (short-term memory) and were most robust 15 min after ingestion of barley and potato and 60 min after ingestion of glucose.

Overall, poor  $\beta$  cell function was associated with improved performance for all 3 carbohydrates compared with placebo, and poorer baseline performance was associated with improvement after potato and barley ingestion. The effects were generally stronger for delayed recall for all carbohydrates, but the strength of the effects at 15 and 60 min varied for each carbohydrate.

The linear regression and 95% mean CI between improvement and  $\beta$  cell function for all 20 subjects for total delayed recall for all 3 carbohydrates are shown in **Figure 3**. Because the regression lines crossed 0 (y axis), the CIs were used to determine whether improvements were significant in subjects with poor  $\beta$  cell function and whether deficits were significant in subjects with good  $\beta$  cell function. CIs for significant correlations clearly indicated significant improvements in subjects with poor  $\beta$  cell function (entire CIs generally exceeded 0) and were suggestive of deficits in subjects with good  $\beta$  cell function. In contrast, when the CIs were examined with respect to the correlations between improvements and baseline performance, significant improvements in subjects with poor baseline performance and significant deficits in subjects with good baseline performance were observed (data not shown). Thus, not only did subjects with poor baseline memories perform better with carbohydrate ingestion, but those with good memories actually performed worse when they consumed carbohydrates.

The response to barley was generally stronger than was the response to glucose or potato. The slopes between improvement and baseline score were stronger for barley than for glucose on 15-min immediate ( $P < 0.0001$ ), delayed ( $P = 0.0029$ ), and total

**TABLE 3**  
Linear and multiple regression analyses for paragraph recall

Improvement with dietary treatment <sup>1</sup>	Baseline score <sup>2</sup>		β Cell function <sup>3</sup>		Multiple regression <sup>4</sup>		
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	Significant predictors	<i>R</i> <sup>2</sup>	<i>P</i>
<b>Glucose<sup>5</sup></b>							
15 Imm	-0.21	NS	-0.27	NS	None	—	—
15 Del	-0.17	NS	-0.46	0.0437 <sup>6</sup>	BC	0.21	0.0437 <sup>6</sup>
15 Tot	-0.20	NS	-0.39	0.0924	BC	0.15	0.0924
60 Imm	-0.10	NS	-0.46	0.0424 <sup>6</sup>	BC	0.21	0.0424 <sup>6</sup>
60 Del	-0.24	NS	-0.42	0.0686	BC	0.17	0.0686
60 Tot	-0.17	NS	-0.47	0.0345 <sup>6</sup>	BC	0.22	0.0345 <sup>6</sup>
Imm tot	-0.17	NS	-0.42	0.0630	BC	0.18	0.0630
Del tot	-0.23	NS	-0.51	0.0217 <sup>6</sup>	BC	0.26	0.0217 <sup>6</sup>
<b>Potato<sup>5</sup></b>							
15 Imm	-0.60	0.0056 <sup>6</sup>	-0.44	0.0526	BS, BC	0.42	0.0094 <sup>6</sup>
15 Del	-0.52	0.0191 <sup>6</sup>	-0.52	0.0188 <sup>6</sup>	BS, BC	0.41	0.0117 <sup>6</sup>
15 Tot	-0.58	0.0072 <sup>6</sup>	-0.49	0.0283 <sup>6</sup>	BS, BC	0.44	0.0073 <sup>6</sup>
60 Imm	0.16	NS	-0.15	NS	None	—	—
60 Del	0.00	NS	-0.15	NS	None	—	—
60 Tot	0.10	NS	-0.16	NS	None	—	—
Imm tot	-0.34	NS	-0.42	0.0680	None	—	—
Del tot	-0.44	0.0533	-0.50	0.0264 <sup>6</sup>	BS, BC	0.33	0.0327 <sup>6</sup>
<b>Barley<sup>5</sup></b>							
15 Imm	-0.76	0.0001 <sup>6</sup>	-0.45	0.0462 <sup>6</sup>	BS, BC, I	0.66	0.0005 <sup>6</sup>
15 Del	-0.63	0.0030 <sup>6</sup>	-0.48	0.0309 <sup>6</sup>	BS, BC, I	0.63	0.0009 <sup>6</sup>
15 Tot	-0.71	0.0004 <sup>6</sup>	-0.48	0.0344 <sup>6</sup>	BS, BC, I	0.66	0.0005 <sup>6</sup>
60 Imm	-0.12	NS	-0.06	NS	None	—	—
60 Del	0.09	NS	-0.15	NS	None	—	—
60 Tot	-0.01	NS	-0.11	NS	None	—	—
Imm tot	-0.69	0.0007 <sup>6</sup>	-0.40	0.0772	BS, BC	0.52	0.0020 <sup>6</sup>
Del tot	-0.53	0.0169 <sup>6</sup>	-0.54	0.0144 <sup>6</sup>	BS, BC	0.43	0.0086 <sup>6</sup>

<sup>1</sup>Improvement = score with food or drink – score with placebo.

<sup>2</sup>Baseline score (BS) = total score on all 4 paragraph recall tests with placebo.

<sup>3</sup>β Cell function (BC) and insulin resistance (I) were calculated from fasting plasma glucose and insulin concentrations by using Homeostasis Model Assessment (40).

<sup>4</sup>Improvement used as response variable and BS, BC, I, and incremental area under the glucose response curve (gAUC) used as predictor variables. The subset of variables with the highest adjusted *R*<sup>2</sup> are given (actual *R*<sup>2</sup> shown in table). Predictors had to meet the 0.1500 significance level to be included in the table.

<sup>5</sup>15 Imm, immediate recall 15 min after consumption; 15 del, delayed recall 15 min after consumption; 15 tot, sum of immediate and delayed recall 15 min after consumption; imm tot, sum of immediate recall of both time points combined; del tot, sum of delayed recall for both time points combined.

<sup>6</sup>*P* ≤ 0.05.

recall (*P* = 0.0002) and on total immediate recall (*P* = 0.0128) and were stronger for barley than for potato on total immediate recall (*P* = 0.0342). The slopes between improvement and β cell function did not differ significantly among glucose, potato, and barley on any test.

Results of regression analyses performed for men and women separately were similar to the overall data and there were no systematic differences between sexes. In general, stronger associations were evident with barley and glucose in women but with potato in men (Figure 3).

*Word list recall*

An association between improvement with dietary treatment and poor glucose regulation was observed for word list recall but was not as robust as for the paragraph recall.

Similar to paragraph recall, no subject reached ceiling performance. Indeed, even by the third recall of the list, the mean and maximum performance were 6.1 ± 0.1 and 11 (out of 12), respectively.

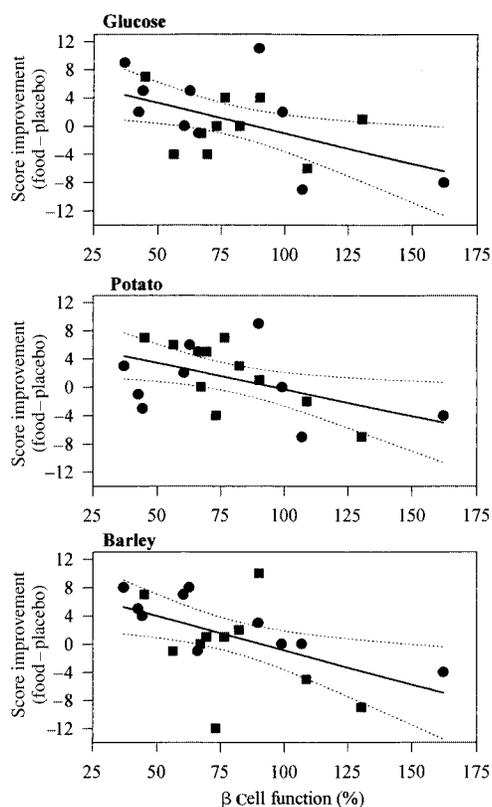
A main effect of time on performance was observed (*P* = 0.0162), indicating that performance at 15 min was better than that at 60 and 105 min (*P* = 0.0092), and an effect of sex (*P* = 0.0305)

indicated that women performed better than did men. Not surprisingly, a repeat effect was also evident on word list recall (*P* < 0.0001), indicating that performance was better after more presentations of the list.

The influence of food on the change in score from the first to the second presentation of the word lists, from the second to the third presentation, and from the first to the third presentation were analyzed to capture a measure of learning. In general, there was a trend for all 3 carbohydrates to be beneficial compared with placebo from the first to the second presentation but for placebo to be better from the second to the third presentation and from the first to the third presentation (data not shown). Overall, these data suggest faster learning after carbohydrate ingestion, with catch-up in the placebo group.

Linear regressions between improvement compared with placebo (total score at each time point) and glucose regulation measurements showed that fasting plasma glucose was a better predictor than was baseline score, β cell function, insulin resistance, or gAUC (data not shown). High fasting plasma glucose values correlated significantly with improvements with glucose at 15 min (*r* = 0.45, *P* = 0.0477) and overall (all time points combined: *r* = 0.46, *P* = 0.0397) and with barley at 15 min (*r* = 0.48,





**FIGURE 3.** Linear regression analyses and 95% mean CIs for regression between improvement with food in score on delayed paragraph recall (15 and 60 min tests combined) and  $\beta$  cell function for all 20 subjects. Higher scores represent better performance. Poorer  $\beta$  cell function was associated with improved performance for all 3 carbohydrates compared with placebo.  $r$  and  $P$  values for all subjects were as follows: glucose,  $-0.51$ ,  $0.0217$ ; potato,  $-0.50$ ,  $0.0264$ ; and barley,  $-0.54$ ,  $0.0144$ .  $r$  and  $P$  values for men (■) and women (●) separately were as follows: glucose (men),  $r = -0.21$ ,  $P = 0.5659$ ; glucose (women),  $r = -0.63$ ,  $P = 0.0496$ ; potato (men),  $r = -0.76$ ,  $P = 0.0107$ ; potato (women),  $r = -0.35$ ,  $P = 0.3215$ ; barley (men),  $r = -0.43$ ,  $P = 0.2153$ ; and barley (women)  $r = -0.80$ ,  $P = 0.0051$ .

$P = 0.0307$ ). No consistent strong associations were observed when men and women were analyzed separately (data not shown).

#### Visuomotor test

In general, the results of the visuomotor test were similar to those of the paragraph recall test. Poor  $\beta$  cell function was associated with greater improvements in visuomotor performance (Trails) with all 3 carbohydrates compared with placebo and there was a trend for subjects with good insulin sensitivity (low insulin resistance) to improve with food. These associations were much stronger in women than in men.

There were no significant main effects of food on Trails performance. There was a significant effect of time ( $P = 0.0007$ ): performance at 105 min was better than at 15 min ( $P = 0.0019$ ) or 60 min ( $P = 0.0204$ ).

Linear and multiple regression analyses were performed using percentage improvement with each food  $\{[(\text{food score} - \text{placebo score})/\text{placebo score}] \times 100\}$  as the response variable and baseline score (combined placebo score on all 3 Trails tests: 15, 60, and 105 min),  $\beta$  cell function, insulin resistance, and gAUC as

predictor variables. It is important to note that a lower score (shorter time) on this test represents better (faster) performance. The risk of observing regression to the mean by comparing baseline score with improvement with food was determined to be minimal because baseline scores were highly correlated with total Trails scores with each of the other dietary treatments ( $r > 0.76$ ,  $P < 0.0001$  for all 3 carbohydrates).

Linear correlations between percentage improvement and  $\beta$  cell function and between percentage improvement and insulin resistance are shown for each of the three Trails tests and for total score in **Table 4**. Several strong associations between poor  $\beta$  cell function and improved performance and between good insulin sensitivity and improved performance were observed for all 3 carbohydrates. A high gAUC was associated with improved performance for barley only (data not shown). There were no significant correlations between improvement and baseline score ( $P > 0.05$ ). Multiple regression analyses indicated that in general, relatively poor  $\beta$  cell function and baseline performance, high gAUC, and good insulin sensitivity were associated with improvement in performance on various measures of this task (Table 4).

The linear regression and 95% mean CIs between percentage improvement and  $\beta$  cell function for all 20 subjects at 60 min are shown in **Figure 4**. CIs indicated that poor  $\beta$  cell function was generally associated with improved performance after carbohydrate consumption, whereas good  $\beta$  cell function was associated with poor performance after carbohydrate consumption (the entire CIs were  $>0$  for good  $\beta$  cell function). Thus, similarly to the results obtained for paragraph recall, not only did subjects with poor  $\beta$  cell function improve after carbohydrate ingestion, but those with good  $\beta$  cell function actually performed worse when they consumed carbohydrates.

The associations between improvement and  $\beta$  cell function and between improvement and gAUC were generally stronger for barley and glucose than for potato (data not shown). The slopes between improvement and insulin resistance did not differ significantly among glucose, potato, and barley on any test.

Separate regression analyses for men and women showed similar results as the overall data for women only; there were no significant associations for men (data not shown). The  $r$  and  $P$  values for women were generally stronger than the overall associations because of the lack of a strong association in men.

#### Attention test

No main effects of food on the attention task were found; however, a barley  $\times$  sex interaction ( $P = 0.0261$ ) was observed, showing that women performed better with barley than with placebo ( $P = 0.0135$ ).

Linear regression analyses between improvement with each food and baseline score,  $\beta$  function, insulin resistance, and gAUC showed no significant associations, except that baseline score was associated with improvement with barley ( $r = -0.55$ ,  $P = 0.0128$ ), suggesting that subjects with poor attention improved with barley only. This same relation was significant for men ( $r = -0.80$ ,  $P = 0.0060$ ) but not for women. Thus, overall, men with poor baseline attention and all women performed better with barley than with placebo.

## DISCUSSION

The present study is the first to show that cognitive performance is associated with glucose regulation in the elderly before

**TABLE 4**  
Linear and multiple regression analyses for visuomotor test

Percentage improvement with dietary treatment <sup>1</sup>	β Cell function <sup>2</sup>		Insulin resistance <sup>2</sup>		Multiple regression <sup>3</sup>		
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	Significant predictors	<i>R</i> <sup>2</sup>	<i>P</i>
<b>Glucose</b>							
15 min	0.44	0.0520	0.21	NS	BC	0.19	0.0520
60 min	0.60	0.0051 <sup>d</sup>	0.59	0.0067 <sup>d</sup>	BC, I	0.41	0.0120 <sup>d</sup>
105 min	0.19	NS	0.13	NS	gAUC	0.12	0.1317
Total	0.55	0.0125 <sup>d</sup>	0.40	0.0813	BC, gAUC	0.36	0.0231 <sup>d</sup>
<b>Potato</b>							
15 min	0.09	NS	0.06	NS	None	—	—
60 min	0.52	0.0198 <sup>d</sup>	0.40	0.0782	BC, BS, gAUC	0.43	0.0253 <sup>d</sup>
105 min	-0.12	NS	0.12	NS	None	—	—
Total	0.25	NS	0.28	NS	None	—	—
<b>Barley</b>							
15 min	0.62	0.0032 <sup>d</sup>	0.52	0.0197 <sup>d</sup>	BC, BS	0.44	0.0067 <sup>d</sup>
60 min	0.45	0.0454 <sup>d</sup>	0.41	0.0729	BC	0.20	0.0454 <sup>d</sup>
105 min	0.10	NS	-0.03	NS	gAUC	0.26	0.0211 <sup>d</sup>
Total	0.52	0.0178 <sup>d</sup>	0.39	0.0932	BC, gAUC	0.39	0.0142 <sup>d</sup>

<sup>1</sup> [(Score with food or drink - score with placebo)/score with placebo] × 100. A lower score (faster) represents better performance.

<sup>2</sup> β Cell function (BC) and insulin resistance (I) were calculated from fasting plasma glucose and insulin concentrations by using Homeostasis Model Assessment (40).

<sup>3</sup> Percentage improvement used as response variable and baseline score (BS), BC, I, and incremental area under the glucose response curve (gAUC) used as predictor variables. The subset of variables with the highest adjusted *R*<sup>2</sup> are given (actual *R*<sup>2</sup> shown in table). Predictors had to meet the 0.1500 significance level to be included in the table.

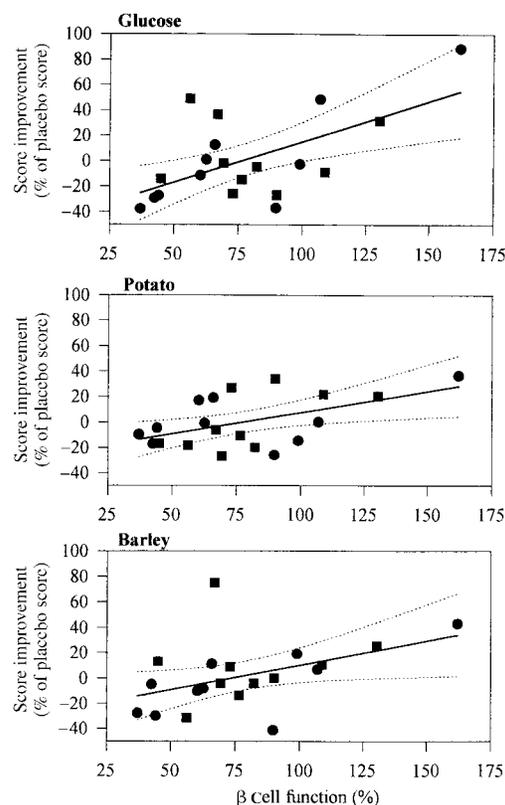
<sup>4</sup> *P* ≤ 0.05.

the diagnosis of impaired glucose tolerance and that, in addition to glucose, common carbohydrate-containing foods can improve cognition. Importantly, the carbohydrate-enhancing effects of these foods were independent of their effects on plasma glucose.

High gAUC, poor β cell function, good insulin sensitivity, and low BMI were associated with poor baseline short- and long-term verbal declarative memory and visuomotor performance in cognitively intact elderly subjects with normal fasting plasma glucose. The consumption of 50 g carbohydrate as glucose, potatoes, or barley improved verbal declarative memory in individuals with poor baseline memory or poor β cell function and improved performance on a visuomotor task in those with poor β cell function. Thus, individuals with relatively poor glucose regulation performed worse on cognitive tests than did those with better regulation and were most sensitive to the cognitive-enhancing effects of carbohydrates.

Although no subject obtained the maximum score on any test, it is possible that subjects with good memories had reached their upper capacities of performance at baseline. Thus, these subjects may not have had room for improvement after carbohydrate ingestion. However, it is unlikely that a ceiling effect explains why these individuals did not benefit from carbohydrates, because they actually showed a deficit in performance with carbohydrate consumption.

In the present study, glucose regulation was associated with cognition in healthy elderly subjects, extending previous findings indicating that persons with type 2 diabetes (4) and impaired glucose tolerance (5, 6) perform worse on cognitive tests than do those with better regulation. The novelty of the present study, the results of which are strengthened by a recent report in young adults (12), is that the relation was observed in subjects with normal glucose tolerance. Although a cause-and-effect relation cannot be established, the glucose regulatory profile of the subjects who showed poorer performance is consistent with the pathogenesis of type 2 diabetes in nonobese individuals (44), strongly



**FIGURE 4.** Linear regression analyses and 95% mean CIs for regression between improvement with food in score on Trails at 60 min and β cell function for all 20 subjects. A lower percentage represents better performance. Data points for men (■) and women (●) are shown for comparison. Poorer β-cell function was associated with better performance for all 3 carbohydrates compared with placebo. *r* and *P* values for all subjects were as follows: glucose, *r* = 0.60, *P* = 0.0051; potato, *r* = 0.52, *P* = 0.0198; and barley, *r* = 0.45, *P* = 0.0454.

suggesting that brain function may already be impaired in very early stages of glucose dysregulation. Thus, preventing the development of impaired glucose regulation, possibly through dietary means, may help prevent cognitive decline. For instance, reducing saturated fat intake, which is associated with poor glucose regulation (45) and cognition (46–50), may be beneficial (51).

Several investigators have shown that a glucose drink improves memory in rodents and humans (15). The results of the present study show that glucose may not be special in this respect because consumption of the same amount of carbohydrate as a high-GI food (potato) or a low-GI food (barley) produced similar cognitive-enhancing effects. In fact, a stronger relation between baseline performance and memory improvement was observed for barley than for glucose or potato, suggesting that low-GI foods may actually have greater benefits.

The effects of carbohydrates on cognitive performance appear to be specific to a subgroup of individuals and to particular cognitive tasks (15). Several studies, including this one, showed that individuals with poor glucose regulation may be more sensitive to the cognitive-enhancing effects of glucose than are individuals with better regulation (52). Consistent with these data, the present data also suggest that glucose and other carbohydrates have a stronger effect on functions mediated by the medial temporal lobe, such as long-term verbal declarative memory (8, 10, 16, 20, 23, 28, 29), than those mediated by other brain regions, such as short-term or working memory (8, 16, 23), procedural memory (16, 22, 23), or response inhibition (23, 53). The carbohydrate effects were stronger for the long-term than for the short-term memory tests, which are mediated by the prefrontal lobe (54), and minimal effects were seen on the attention task (mediated by a neural network including the parietal and frontal lobes; 55). Nevertheless, other brain regions may also be influenced, albeit to a lesser extent (56).

Performance on Trails, which involves several brain regions, was improved in subjects with poor  $\beta$  cell function, and there was a trend for word list learning, mediated by the frontal lobe (57), to be initially improved with carbohydrates. These Trails data differ from those of another study (56), but alternative versions of the task and different measures of glucose regulation were used in the 2 studies. Thus, carbohydrates may reverse memory deficits and improve performance on difficult tasks and in individuals with poor glucose regulation but may have lesser effects on easy tasks and in subjects with good memories and good glucose regulation.

A better measure of glucose regulation (HOMA) was used in this study than in previous studies and extends our understanding of the subgroup of individuals who may be sensitive to the cognitive-enhancing effects of carbohydrates. Relatively poor  $\beta$  cell function and good insulin sensitivity were correlated with the carbohydrate effects, suggesting that  $\beta$  cell dysfunction (in the absence of insulin resistance) may be the important physiologic factor that predisposes an individual to be sensitive to the effects of carbohydrate. Although the mechanism is not known, the importance of insulin-secreting cells is consistent with the observation that circulating insulin may be important in mediating brain function, independently of glucose (58).

Actual changes in blood glucose concentrations may not be important in mediating cognitive performance unless a very minor change is necessary. Barley (lowest GI) had the strongest and earliest effect on memory performance, even though plasma glucose rose to only 6.0 mmol/L by 15 min. In addition, blood

glucose concentration peaked at 60 min for all 3 carbohydrates, but the strongest effects were not always at this time point. These observations contrast with the hypothesis that the benefits of glucose ingestion are related to blood glucose (52) and that an optimal concentration (8–10 mmol/L) must be obtained (17, 20, 21). Proponents of this hypothesis argue that glucose may exert its effects by affecting the uptake and utilization of glucose by the brain, which could affect neurotransmitters (59, 60).

The fact that all 3 carbohydrates enhanced cognition suggests that the provision of energy rather than the effect on blood glucose may be important. On the basis of animal research showing that vagotomy decreases the memory-enhancing effects of peripherally injected drugs (52) and that fructose, which does not cross the blood-brain barrier, enhances memory (61, 62), it has been suggested that the site of action of glucose may be the liver, which could send a neural signal to the central nervous system. Thus, energy intake may be involved in mediating carbohydrate-induced cognitive improvements, possibly via gut peptides or the vagus nerve.

It is not clear why the carbohydrates had their strongest effects at various time points, but it may relate to the influence of proactive interference [ie, the process through which memory for new material (eg, 60 min) is disrupted by previously learned material (eg, at 15 min)]. Healthy elderly adults are highly susceptible to this interference (63) and an anecdotal observation was that subjects often recalled information from earlier paragraphs and word lists on subsequent tests during the same day. Thus, the dietary treatments may affect proactive interference and therefore differentially influence performance at later time points.

Another issue examined was whether men are more sensitive to the beneficial effects of glucose than are women, which was reported previously (23). The present results do not support this finding because no systematic differences between the sexes were observed for memory performance after carbohydrate intake, and stronger associations were observed for women than for men on the visuomotor task.

An important finding of this study was that subjects with good baseline performance and  $\beta$  cell function generally performed worse after ingesting carbohydrates. Similar findings after glucose consumption in young adults have been reported (23). Thus, carbohydrate ingestion may bring relatively impaired individuals up to an optimal level of functioning but may impair those already at this level.

In summary, high gAUC, poor  $\beta$  cell function, good insulin sensitivity, and low BMI were associated with poor baseline cognitive performance in healthy elderly subjects with normal glucose tolerance. In addition, carbohydrate-containing foods enhanced cognition, similarly to glucose, in subjects with relatively poor memories or poor  $\beta$  cell function. Thus, individuals with seemingly minor deficits in glucose regulation appear to perform worse on cognitive tests and are most sensitive to the beneficial effects of carbohydrates. 

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