Dietary protein, carbohydrate, and fat enhance memory performance in the healthy elderly[1–3]

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ABSTRACT

Background: Dietary carbohydrates can improve memory. Whether these effects are related to elevations in blood glucose or to energy ingestion is unknown.

Objectives: Our objectives were to determine *1*) the influence of isoenergetic protein-, carbohydrate-, and fat-containing drinks on cognitive performance and *2*) whether the time period after ingestion affects cognition.

Design: After fasting overnight, 11 men and 11 women aged 61–79 y consumed either a 300-mL drink containing 774 kJ as pure protein (whey), carbohydrate (glucose), or fat (safflower oil) or a nonenergy placebo on 4 separate mornings. Cognitive tests were administered 15 and 60 min after ingestion of the drinks. Plasma glucose and serum insulin concentrations were measured.

Results: Only the carbohydrate drink increased blood glucose ($P < 0.0001$). Compared with the placebo, all 3 macronutrients improved delayed paragraph recall (PR) ($P < 0.001$) and improved or tended to improve immediate PR ($P < 0.04$) 15 min after ingestion. Beneficial effects on other cognitive tests were confined to one or more of the macronutrients: carbohydrate improved Trail Making Test (Trails) performance at 60 min ($P = 0.02$) and tended to improve Trails at 15 min ($P = 0.04$) and PR at 60 min in men, carbohydrate and fat improved or tended to improve performance on Trails at 15 and 60 min in subjects with poor baseline scores ($r > -0.41$, $P < 0.03$), fat tended to improve attention at 60 min ($P < 0.05$), and protein reduced the rate of forgetting on the PR at 15 min ($P = 0.002$).

Conclusions: Energy intake from protein, carbohydrate, or fat can enhance memory independently of elevations in blood glucose. Each macronutrient may also exert unique effects on cognition. *Am J Clin Nutr* 2001;74:687–93.

KEY WORDS Glucose, carbohydrate, protein, fat, memory, cognition, elderly

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 to prevent or reduce such deficits (1). Current evidence suggests that poor glucose regulation is associated with poor cognitive performance (2–4) and that the consumption of dietary carbohydrates can improve memory in certain situations (5, 6).

See corresponding editorial on page 567.

However, research examining the role of the other macronutrients on cognitive function is lacking (7, 8).

Compared with placebo, a 50-g glucose drink improves memory performance 15–20 min after ingestion most consistently in individuals who have relatively poor memories and glucose regulation (4, 9–13). Blood glucose concentrations between 8 and 10 mmol/L may be optimal for improved memory (13–15), and the effects are most robust on tests of declarative memory (conscious recollections of facts or events) (10, 16–18), which is mediated by the medial temporal lobes and related structures (19). However, we recently found that carbohydrate foods improved memory in the healthy elderly, but the effects were not related to changes in blood glucose (4). Barley, which only raised blood glucose to 6.7 mmol/L, improved memory similarly to glucose and potatoes, which raised blood glucose to ≈9.5 mmol/L. These results suggest that the ingestion of energy, rather than changes in blood glucose concentration, may be involved in the mechanism mediating enhancements in cognitive performance after carbohydrate intake.

In contrast with the glucose studies, few conclusions were made about the effects of protein and fat on cognition (7, 8). Several studies showed that eating breakfast can improve cognitive

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performance compared with omitting breakfast (7, 8), but the effect of each macronutrient was not defined because of various methodologic issues. First, although the effect of meals relatively high in protein, carbohydrate, and fat on cognition was examined, all meals contained some carbohydrate. Because glucose affects cognitive performance, it is impossible to determine whether the effects of mixed macronutrient meals on performance are related to a carbohydrate-induced increase in blood glucose, to another macronutrient, or to energy intake alone. Second, testing was only conducted 30 min to 4 h after ingestion even though the most robust effects of glucose occur 15–20 min after ingestion. Finally, testing was generally limited to children and young adults, possibly concealing potentially beneficial effects of macronutrients in individuals with poorer baseline memory skills, such as the elderly. Thus, the purpose of the present study was to identify the effect of each macronutrient on cognitive performance. This was accomplished by examining the influence of equal-volume, isoenergetic, pure (>98% of energy) protein, carbohydrate, and fat drinks on cognitive performance in healthy elderly people.

SUBJECTS AND METHODS

Subjects

We used a database of previously recruited subjects at the Memory Laboratory of the University of Toronto to contact 11 male and 11 female free-living subjects aged 61–79 y. The subjects participated voluntarily; compensation was provided for travel. All procedures were approved by the ethics committees of the Baycrest Centre for Geriatric Care and the University of Toronto. Only subjects who spoke English as their native language were selected. The level of education ranged from 7 to 12 y, and no subject had evidence of diabetes (fasting plasma glucose ≥7.0 mmol/L; 20) or cognitive decline (a score <25 out of a maximum score of 30 on the Mini-Mental State Examination; 21).

Procedures

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 in the morning on the first day to complete a 30-min screening; on the remaining 3 d, subjects arrived 30 min later. Each subject was tested individually with one test drink (placebo, protein, carbohydrate, or fat) on 4 mornings, each separated by ≈1 wk, and no less than 3 d, to minimize potential carryover effects. The order of the 4 sessions was counterbalanced across test drinks.

During each of the 4 test sessions, blood was collected by finger prick and analyzed for fasting serum insulin at a later date. One additional drop of blood was collected for measurement of fasting plasma glucose. After blood collection, one test drink was given to each subject, who was asked to try to consume the entire amount within ≈5 min. Each subject's plasma glucose was measured 15, 60, and 90 min after the start of consumption of the test drink.

Immediately after the blood collection at 15 min, the subjects underwent 3 verbal memory tests: immediate word list recall and immediate and 20-min delayed paragraph recall. These memory tests were used because glucose was shown to enhance performance on similar tests in healthy elderly subjects (4, 9, 10, 14, 16, 17, 22–25). The subjects were first tested on immediate recall of a narrative word list. Immediately after this test, immediate recall of a narrative paragraph was tested. After a 20-min delay, subjects were tested for recall of the same paragraph. The delay period was filled with nonverbal tasks, including the Trail Making Test (or Trails) Parts A and B Adult Form (26) and an attention test. 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 tests, Trails, and the attention test both 15 and 60 min after the start of consumption of the test drink. The assignment of test versions was counterbalanced across test drinks and time of testing.

Test drinks

Subjects were blinded to the content of the 4 test drinks, all of which contained 300 mL, 774 kJ (except placebo), and lemon juice; were of similar sweetness; and were consumed through a straw from opaque cups. The drinks contained the following: *1*) placebo: 290 mL water, 10 mL lemon juice, and 23.7 mg sodium saccharin (Hermesetas Original; JL Freeman Inc, Boucherville, Canada); *2*) carbohydrate: 260 mL water, 10 mL lemon juice, and 50 g glucose (dextrose monohydrate; Bio-Health, Dawson Traders Ltd, Toronto); *3*) protein: 260 mL water, 10 mL lemon juice, 50.5 g whey protein isolate (Ultimate Balance Whey Protein Isolate; BioAdvantex Pharma, Wilmington, DE), and 23.7 mg sodium saccharin; and *4*) fat: 248.9 mL water, 10 mL lemon juice, 41.1 g microlipid (50% safflower oil emulsion; Mead Johnson Nutritionals, Evansville, IN), and 23.7 mg sodium saccharin. The percentages of energy from each macronutrient (manufacturers' analyses) for the 4 test drinks were as follows: *1*) placebo: 0 kJ; *2*) carbohydrate: 100% as carbohydrate; *3*) protein: 98.4% as protein, 1.1% as carbohydrate, and 0.3% as fat; and *4*) fat: 100% as fat.

Cognitive tests

Memory tests

Word list recall was used to test a form of verbal declarative memory, which is demonstrated by the recall of material immediately after it is presented and is of limited capacity; the information can only be held for a few minutes (27). Eight versions of a modified Rey Auditory-Verbal Learning Test (28) were developed (4), each consisting of one list containing 12 unrelated, but familiar, 2-syllable nouns. Each list was recorded on audiotape; words were spoken at a rate of ≈1/s. Subjects listened to the same list 3 times in succession and were asked to immediately recall as many words as possible. 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 (28).

For paragraph recall, memory was assessed immediately after presentation and after a 20-min delay. Overall paragraph recall performance (immediate + delayed) and forgetting (immediate − delayed) were also assessed. Eight paragraphs of comparable difficulty, length, and context, similar to the Logical Memory subtest of the *Wechsler Memory Scale—Revised* (29), were used as described previously (4). Subjects listened to one paragraph on audiotape and were immediately asked to recall as much of the story as they could. After a 20-min delay, the subjects were again asked to recall as much as they could from the paragraph. The subjects' answers were recorded on audiotape. Subjects

TABLE 1
Characteristics of subjects[1]

	All subjects (n = 22)	Men (n = 11)	Women (n = 11)
Age (y)	71.2 ± 1.3	70.0 ± 1.6	72.4 ± 2.2
Education level (grade)	10.5 ± 0.3	10.2 ± 0.4	10.7 ± 0.5
MMSE score (maximum: 30)	28.2 ± 0.3	27.7 ± 0.4	28.6 ± 0.3
BMI (kg/m^2)	25.6 ± 0.6	25.6 ± 0.7	25.6 ± 0.9
Fasting plasma glucose (mmol/L)	5.2 ± 0.1	5.3 ± 0.1	5.2 ± 0.1
Fasting serum insulin (pmol/L)	51.9 ± 5.5	50.1 ± 8.9	53.6 ± 6.8
β Cell function (%)[2]	82.4 ± 7.5	75.9 ± 11.7	88.8 ± 9.6
Insulin resistance[2]	1.70 ± 0.90	1.66 ± 0.31	1.74 ± 0.24
gAUC (mmol·min/L)[3]	731.6 ± 23.3	730.6 ± 24.7	732.6 ± 40.9

[1] $\bar{x}$ ± SEM. MMSE, Mini-Mental State Examination; gAUC, total area under the glucose response curve. There were no significant differences between men and women.
[2] Calculated from fasting plasma glucose and insulin concentrations with use of the homeostasis model assessment (30).
[3] Values were determined from plasma glucose concentrations 0, 15, 60, and 90 min after ingestion of a 50-g glucose drink.

were distracted with nonverbal stimuli (Trails and attention tests) during the delay period to discourage rehearsing.

Trails test

Twelve alternative versions of the standard Trails Parts A and B Adult Form (26) were used (original plus 11 new versions). This test measures speed for visual search, attention, mental flexibility, and motor function and is a sound measure of general brain functions (28). For part A, subjects are required to connect 25 encircled numbers, somewhat randomly arranged on a page, in proper order (from 1 to 25) as quickly as they can. This measures visual motor speed. For part B, 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. Subjects were corrected by the experimenter when mistakes were made; the timer was not stopped during this time. Standard scoring methods were used to assess performance: the time to complete part A, part B, and parts A and B combined (faster times represent better scores) and the difference between the times necessary to complete parts A and B (B − A), which is sensitive to frontal lobe function (smaller differences represent better scores).

Attention test

Subjects watched 1 of 4 episodes of a popular situation comedy on videotape during each of the 4 sessions. Subjects watched the first 10 min of each episode during the first delay period (after the tests at 15 min) and the last 10 min during the second delay period (after the tests at 60 min). While watching the television program, the subjects were asked to keep track of, by marking on a page, the number of times specific words were spoken and the number of times doors opened and closed. The percentages correct over the first 10 min, the second 10 min, and the entire 20-min episode were used as the scores on this test.

Blood glucose and insulin analyses

Blood was collected by finger prick with a Penlet II Automatic Blood Sampler lancet device (Lifescan Canada Ltd, Mississauga, Canada). Plasma glucose was measured by using a blood glucose meter (One Touch Basic Meter; Lifescan Canada Ltd). Serum was pooled for each subject, and insulin was analyzed by the Banting and Best Diabetes Core Laboratory, University of Toronto, by using a radioimmunoassay as described previously (4). Homeostasis model assessment was used to estimate β cell function and insulin resistance from fasting plasma glucose (average of all 4 sessions) and insulin concentrations (30). The total area under the glucose response curve was determined from the plasma glucose values obtained after the consumption of the glucose drink.

Statistical analyses

Statistical analyses were conducted with SAS 6.12 (SAS Institute, Inc, Cary, NC). Repeated-measures analysis of variance was used to determine the influence of drink, 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 drink compared with placebo. Linear and multiple regression analyses were conducted to examine the relation between baseline cognitive performance and glucose regulation and between baseline cognitive performance and the response to each drink. An analysis of the risk of regression to the mean (31) was conducted to determine the appropriateness of regressing baseline performance against the improvement with drink. Statistical significance was set at $P < 0.05$, except when the Bonferroni correction was used for multiple comparisons, in which case statistical significance was set at $P < 0.02$.

RESULTS

Characteristics of drink ingestion and effects on blood glucose

All subjects consumed each of the 4 drinks within 7 min ($\bar{x}$ ± SD: 2.9 ± 1.4 min). No significant differences in the time taken to consume the drinks were observed. One male subject only consumed two-thirds of the protein drink; therefore his cognitive performance data after protein ingestion were excluded from all analyses. On a palatability scale of 0 (very pleasant) to 10 (not at all pleasant), the glucose drink was rated by the subjects as more palatable ($\bar{x}$ ± SEM: 3.4 ± 0.4) than the other 3 drinks (placebo: 4.9 ± 0.5; fat: 5.8 ± 0.6; protein: 5.9 ± 0.6; $P < 0.006$).

Subject characteristics and glucose regulation measurements are reported in **Table 1**. All subjects had normal fasting plasma glucose values (<6.1 mmol/L; 20). No significant differences in any of these measures were evident between men and women. As expected, only glucose ingestion caused a significant rise in plasma glucose concentration compared with that after ingestion

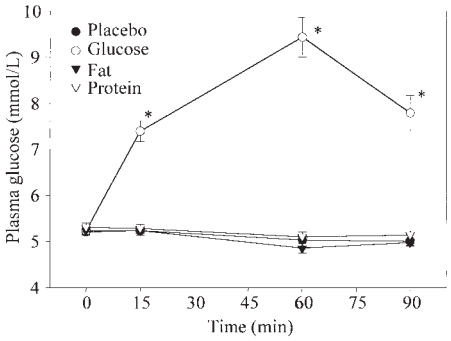

FIGURE 1. Mean (±SEM) plasma glucose concentrations in response to the placebo, glucose, fat, and protein test drinks for men and women combined ($n = 21$). *Significantly different from placebo, $P < 0.0001$. The incremental area under the curve was greater after glucose ingestion than after ingestion of the other drinks ($P < 0.0001$).

of placebo (at each time point and as the incremental area under the curve; **Figure 1**).

Relation between glucose regulation and baseline cognitive performance

The relation between measures of glucose regulation and baseline (placebo) cognitive performance was examined because previous studies showed that relatively poor glucose regulation is associated with poor cognitive performance in healthy subjects (3, 4). Total placebo scores (combining scores at all time points) on each cognitive test were used as the response variables (baseline score), and body mass index, the total area under the glucose response curve, β cell function, and insulin resistance were used as the predictor variables. There were no significant associations for any of the cognitive tests.

Effects of test drinks on cognitive performance

Paragraph recall

Data from one female subject were excluded from the analyses of performance 15 min after ingestion of the fat drink because she had misinterpreted the instructions. The top score was 21 of 25; no subject reached ceiling performance. All subjects were analyzed together because no main effect of sex or interactions with sex was observed. Repeated-measures analysis of variance showed a main effect of drink ($P = 0.01$); an effect of delay ($P = 0.0003$), indicating that performance was better on immediate recall than on delayed recall; a drink × time interaction ($P = 0.03$), indicating that the effect of drink ingestion was dependent on the time of testing (15 or 60 min after ingestion); a trend for a drink × delay interaction, suggesting that the effect of drink ingestion was dependent on the test (immediate or delayed recall); and a drink × time × delay interaction ($P = 0.03$).

Contrast analyses, with significance set at $P < 0.02$ (Bonferroni correction), showed that the ingestion of all 3 macronutrient drinks improved delayed recall (protein: $P < 0.0001$; glucose: $P = 0.001$; fat: $P = 0.0006$) and improved or tended to improve immediate recall (protein: P for trend = 0.04; glucose: $P = 0.02$; fat: $P = 0.008$) compared with the ingestion of placebo 15 min after consumption (**Figure 2**). Importantly, the improvements were stronger for each drink on delayed recall than on immediate recall. Analyses of the difference between immediate and delayed recall (forgetting) showed that there was less forgetting 15 min after protein ingestion than after placebo ingestion ($P = 0.002$). Glucose and fat ingestion led to the same rate of forgetting as did the placebo ingestion at 15 min.

In contrast with the data at 15 min, no effect of drink on paragraph recall was found 60 min after ingestion. However, there was a trend for only the glucose drink to improve performance on the composite score (immediate + delayed) when analyzed as the percentage of improvement compared with placebo (Figure 2). Rate of forgetting at 60 min did not differ on the basis of the type of drink consumed.

Word list recall

Data for one male subject from the first repetition of the word list 15 min after fat ingestion were excluded from the analyses because he had difficulty hearing the list. No main effect of drink was observed. A main effect of time ($P = 0.02$) indicated that performance at 15 min was better than that at 60 min, and a repeat effect ($P < 0.0001$) indicated that, not surprisingly, performance improved after more presentations of the list. The mean (±SD) scores on the first, second, and third repetitions of the list for all data combined were 4.6 ± 1.1, 6.0 ± 1.6, and 7.0 ± 1.8, respectively, at 15 min and 4.3 ± 1.2, 5.7 ± 1.5, and 6.7 ± 1.6, respectively, at 60 min; the possible maximum score was 12. The highest score was 11; no subject reached ceiling performance.

A drink × sex interaction ($P = 0.01$) and a drink × time × repeat × sex interaction ($P = 0.01$) were observed. Contrast analyses, with significance set at $P < 0.02$ (Bonferroni correction), showed that fat ingestion led to impaired performance on total recall (all 3 lists combined) compared with placebo ingestion at 60 min ($P = 0.02$). There was a trend for glucose ingestion to lead to an overall (word lists at 15 and 60 min combined) impairment of performance compared with placebo ingestion in men only ($P = 0.03$). No effect of drink on learning (improvements from list 1 to 2, 2 to 3, and 1 to 3) was observed.

Trails test

No main effect of drink was observed. Performance was better at 60 than at 15 min ($P = 0.02$), and as expected, performance

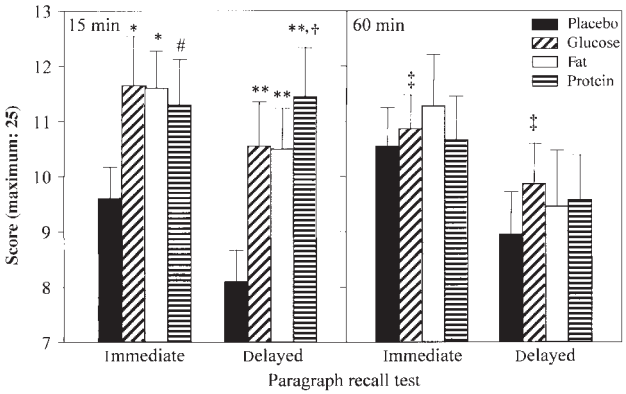

FIGURE 2. Mean (±SEM) scores on the immediate and delayed paragraph recall test 15 ($n = 20$) and 60 ($n = 21$) min after consumption of the placebo, glucose, fat, and protein test drinks for men and women combined. *,#,**,†,‡Significantly different from placebo: *$P \leq 0.02$, #P for trend = 0.04, **$P \leq 0.001$, †$P = 0.002$ (rate of forgetting, immediate − delayed), ‡P for trend = 0.09 (for composite score, immediate + delayed).

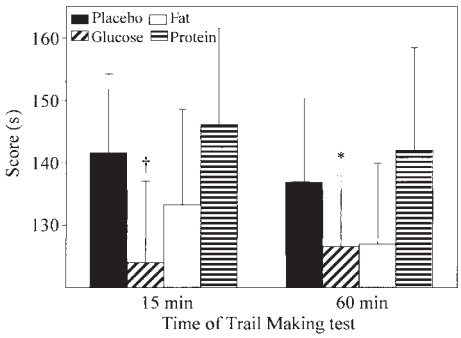

FIGURE 3. Mean (±SEM) scores on the Trail Making Test (parts A + B) in men (n = 10) at 15 and 60 min after ingestion of the placebo, glucose, fat, and protein test drinks. Lower scores represent better performance. †,*Significantly different from placebo: †P for trend = 0.04, *P = 0.02.

on part A was better than on part B ($P < 0.0001$). The mean (±SD) time for all data combined was 48 ± 15 s for part A at 15 min, 47 ± 14 s for part A at 60 min, 98 ± 37 s for part B at 15 min, and 92 ± 32 s for part B at 60 min.

A drink × sex interaction was observed (P = 0.02). Further analyses, with significance set at $P < 0.02$ (Bonferroni correction), showed that both fat and glucose ingestion improved performance compared with placebo ingestion in men on part A at 15 min (P = 0.02). Improvements in overall performance (parts A + B) were confined to glucose in men at both 15 and 60 min after ingestion compared with placebo (**Figure 3**).

The relation between baseline scores and improvement with each test drink was analyzed because previous studies showed that carbohydrates selectively improve cognitive performance in individuals with relatively poor baseline cognitive function (4). Statistical significance was set at $P < 0.02$ (Bonferroni correction). Strong associations between poor baseline performance (overall placebo score on parts A + B at 15 and 60 min combined) and improvement with glucose and fat were observed on several tests. No associations were observed for protein. Significant associations between baseline performance and improvement with glucose were observed for the total score (A + B) at 15 ($r = -0.54$, $P = 0.009$) and 60 ($r = -0.62$, $P = 0.002$) min, for part B at 15 ($r = -0.67$, $P = 0.0007$) and 60 ($r = -0.73$, $P < 0.0001$) min, and for the difference (B − A) at 15 ($r = -0.63$, $P = 0.002$) and 60 ($r = -0.69$, $P = 0.0004$) min. Similar associations were observed for fat: total score (A + B) at 15 ($r = -0.43$, P for trend = 0.04) and 60 ($r = -0.67$, $P = 0.0007$) min, part B at 15 ($r = -0.47$, P for trend = 0.03) and 60 ($r = -0.62$, $P = 0.002$) min, and B − A at 15 ($r = -0.41$, P for trend < 0.05) and 60 ($r = -0.50$, $P = 0.02$) min. Importantly, no relations were observed at 15 or 60 min on part A. The risk of observing regression to the mean by comparing baseline score with improvement with each drink was determined to be minimal because baseline scores were highly correlated with total Trails scores for each of the other test drinks ($r > 0.70$ and $P < 0.0003$ for all 3 drinks).

Attention test

Data from one female subject were excluded from the analyses of performance after ingestion of the fat drink because she had misinterpreted the instructions. All subjects were analyzed together because no main effect of sex or interactions with sex was observed. There was no main effect of drink; however, there was a drink × time effect ($P < 0.05$). The performance of subjects at 15 min did not differ on the basis of the type of drink consumed, but there was a trend for performance to be improved with the fat drink at 60 min compared with placebo ($P < 0.05$). The mean (±SD) percentage correct for all data combined was 66 ± 15% at 15 min and 64 ± 12% at 60 min. The highest score was 96%; no subject reached ceiling performance.

DISCUSSION

To our knowledge, the present study is the first to show that pure dietary protein, carbohydrate, and fat all enhance memory performance. The finding that protein and fat enhanced memory was novel, whereas the benefits of glucose are supported by numerous studies in humans and animals (5, 6). Several studies showed that consuming a mixed macronutrient breakfast can improve cognition compared with not eating breakfast, but some carbohydrate was always included in the meal, with the assumption that blood glucose must increase for an improvement to be observed (7, 8). The effects in the present study were clearly independent of increases in blood glucose concentration because it was not affected by protein or fat intake. Thus, the ingestion of energy, regardless of source, appears to improve memory.

Although several authors consistently showed that a glucose drink improves memory in the healthy elderly compared with placebo (4, 9, 10, 14, 16, 17, 22–25), the mechanism remains to be elucidated. One common hypothesis is that glucose ingestion may improve memory by increasing plasma glucose concentrations, leading to alterations in glucose uptake and utilization by the brain and ultimately to an increase in glucose-mediated synthesis of acetylcholine in the hippocampus region (32, 33). Evidence in rodents supports this acetylcholine hypothesis (34–36). Others have suggested that the insulin response to an increase in glucose may be responsible for the effects on memory (37, 38). Kaplan et al (4) recently showed that a low glycemic index carbohydrate (barley), which minimally elevates blood glucose (39), improves memory similarly to high glycemic index carbohydrates (glucose and potatoes), which suggests that energy ingestion could be responsible for the effects. Importantly, our present finding that the ingestion of energy can improve memory independently of elevations in blood glucose does not rule out the acetylcholine or insulin hypotheses but instead suggests that macronutrients may affect cognition by more than one mechanism.

The fact that memory was enhanced soon after the ingestion of energy from any macronutrient may be explained from an evolutionary perspective. A mechanism that would allow an animal to remember the details of a successful hunt for food would clearly be beneficial for survival (40). Any potential mechanism must be consistent with the finding that glucose, protein, and fat all enhanced memory 15 min after ingestion. Within this time period, which precedes fat absorption, activation of the gut-brain axis probably plays an important role (41). Several gut peptides, including cholecystokinin (40) and gastrin-releasing peptide, pancreastatin, and amylin (42), influence memory in rodents, probably via stimulation of ascending fibers of the vagus nerve (40). Indeed, electrical stimulation of the vagus in human subjects improves declarative memory (43), and vagotomy decreases the memory-enhancing effects of glucose (44) and peripherally injected drugs (40). Thus, memory may have been enhanced by all 3 macronutrients via gut-mediated responses, explaining the nonnutrient-specific improvements observed.

Although all of the macronutrients improved paragraph recall 15 min after ingestion, suggesting that energy intake can enhance specific aspects of cognition, other results from this study suggest additional macronutrient-specific effects. That is, in addition to the effects of energy ingestion on memory, each macronutrient enhanced performance on various tasks, possibly via unique mechanisms. For instance, all 3 macronutrients led to an initial, robust improvement on delayed paragraph recall; however, only glucose ingestion trended toward a sustained (60 min) improvement on this task, which is mediated by the medial temporal lobes (19). Furthermore, for men, only those who ingested glucose had an overall improvement on Trails, supporting the notion that glucose may exert unique effects. The fact that the effect was limited to men is consistent with previous data and may be related to hormonal differences (17).

Whereas an overall improvement on Trails was confined to those who ingested glucose, both fat and glucose, but not protein, improved performance on Trails in subjects with poor baseline scores. Importantly, the strongest benefits of glucose and fat were on part B and on the difference between parts B and A, which is sensitive to frontal lobe function (45), compared with part A alone, which measures visuomotor ability. In addition, at 60 min, fat was the only macronutrient that tended to enhance attention, which is mediated by a neural network including the frontal and parietal lobes (46).

In contrast with glucose and fat, protein was the only macronutrient to influence the rate of forgetting on the paragraph recall test at 15 min; the rate of forgetting is associated with both the medial temporal and diencephalic regions (47). Indeed, after protein ingestion, subjects surprisingly remembered more information during delayed recall than during immediate recall. This finding suggests that some aspect of memory, not shown by the immediate and delayed recall scores, may be enhanced by protein. The immediate, delayed, and forgetting scores all measure aspects of encoding, storage, and retrieval processes to different extents. The inclusion of very specific cognitive tasks in future experiments will be required to decipher the relevance of each aspect of memory.

No benefits of macronutrient ingestion were observed on immediate word list recall, which is mediated by the frontal and medial temporal lobes (48). Although the lack of a benefit on this task is consistent with the glucose studies (10, 16, 17), fat ingestion surprisingly led to an impairment on overall recall at 60 min, and there was a trend for glucose to lead to an impairment in men when the scores at 15 and 60 min were combined. It is unclear why an impairment was observed. In light of the multiple comparisons examined, including the effects on each repeat of each list at 15 and 60 min, total scores at both times, and learning over each repeat of the lists, further research is needed to determine whether these findings are anomalous or reproducible. Although the impairment on immediate word list recall seems contradictory to the effects observed on the other frontal lobe tasks, it must be realized that each task involves several brain regions. Thus, the effects of macronutrient ingestion may be somewhat task-specific depending on the contribution of each brain region.

The activation of the gut-brain axis as well as centrally acting postabsorptive signals, especially at 60 min, may explain the nutrient-specific effects. Specific gut signals may be involved because each macronutrient releases a different profile of peptides; such signals probably occurred throughout the duration of testing because complete gastric emptying of all drinks was estimated to take 60 min (41). By 60 min, significant absorption of glucose and amino acids, but minimal absorption of fat, would have occurred. The prolonged elevation of blood glucose may have influenced the synthesis of brain neurotransmitters, including acetylcholine (32, 33), explaining the sustained benefits of glucose. Insulin, which can improve memory in humans (37, 38), and serotonin, which affects cognition (49), may also be involved. Indeed, within 20–60 min of ingestion, protein increases hypothalamic extracellular amino acid concentrations (50), and each macronutrient differentially affects hypothalamic insulin (51, 52) and serotonin in rats (53), independently of plasma insulin (52). Thus, although the ingestion of energy alone may influence cognition by one mechanism, each macronutrient may improve performance via additional distinct mechanisms involving gut peptides and centrally acting signals.

The relation between glucose regulation and cognition was investigated in this study. Previous research in healthy and diabetic subjects showed that as glucose regulation worsens, memory performance also worsens (2, 3). We recently found a relation between glucose regulation and baseline memory in a healthy elderly population similar to the one in the present study (4). The reason for the failure to observe a similar relation in this study is not clear but may have been due to the greater homogeneity of baseline memory scores in this study (CV in the present study: 28%; CV in the previous study: 40%). Thus, a greater spread in baseline scores may be necessary to observe the association between glucose regulation and baseline scores.

In summary, the ingestion of pure protein, carbohydrate, and fat all improved memory performance 15 min after ingestion in healthy elderly humans. In contrast with the common hypothesis that blood glucose concentrations must be elevated for memory to be improved, these data suggest that the ingestion of energy, in the absence of elevations in blood glucose, can improve memory. In addition, each macronutrient may potentially affect cognition by additional, unique mechanisms.

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