Carbohydrate-Induced Memory Impairment in Adults With Type 2 Diabetes

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OBJECTIVE — Memory impairment is observed in adults with type 2 diabetes. The focus of this study was to determine whether acute carbohydrate consumption contributes to or exacerbates memory dysfunction.

RESEARCH DESIGN AND METHODS — The impact of consuming 50 g of rapidly absorbed carbohydrate (one half bagel and white grape juice) at breakfast was examined in 19 adults with type 2 diabetes. Subjects (mean age 63 ± 9 years, mean BMI 26.1 ± 4.5 kg/m^2) were tested, under fed and fasted conditions, on verbal declarative memory using both word list and paragraph recall tests (immediate and delayed [7-min] recall), Trails Test Part B as a measure of general brain function, and mood (subjectively monitoring global vigor and affect).

RESULTS — Under baseline (fasting) conditions, elevated blood HbA_{1c} was negatively associated with immediate and delayed paragraph recall performance ($R^2 = 0.30$; $P = 0.024$) and higher fasting blood glucose trended toward poorer word list recall ($R^2 = 0.09$; $P = 0.102$). Carbohydrate ingestion influenced measures of delayed, but not immediate, recall in a time-dependent fashion (time × food) (word list, $P = 0.046$; paragraph, $P = 0.044$) such that delayed recall was improved at 15 min postingestion but was impaired at 30 min. Neither Trails Test scores ($P = 0.17$) nor mood (affect, $P = 0.68$ and vigor, $P = 0.45$) were influenced by food ingestion.

CONCLUSIONS — In adults with type 2 diabetes, poorer glycemic control is associated with lower performance on tests of declarative memory. Acute ingestion of high glycemic index carbohydrate foods further contributes to the underlying memory impairment.

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Adults with type 2 diabetes are at increased risk for cognitive decline and dementia (1,2), with the most consistently reported deficits observed on tests of declarative memory (conscious recollections of facts or events). Epidemiologic studies (3,4) estimate that risk of dementia is almost doubled in adults with type 2 diabetes. This increased risk is not confined to dementia of vascular origin but encompasses all types of dementia, including Alzheimer's disease. Therefore, factors beyond hypertension, hyperlipidemia, and microvascular complications, prevalent in the type 2 diabetic population and associated with vascular dementia, must contribute to cognitive decline.

Intervention trials demonstrating enhanced cognitive performance after improvements in glycemic control (2) strengthen the argument that metabolic disturbances of type 2 diabetes contribute, in part, to cognitive deficits. Indeed, poorer performance on cognitive tasks is already observed in individuals without diabetes but with declining glucose tolerance (5–8). That is, reversible cognitive deficits are reported throughout the continuum of declining glucose regulatory status, suggestive of a cause-and-effect relationship.

Whereas glucose regulatory status is associated with cognitive capabilities, it is also predictive of an individual's response to an acute glucose load. Numerous studies have reported that glucose-containing drinks enhance cognitive performance in nondiabetic individuals, with the most robust effects being observed in subjects with memory deficits and/or impaired glucose regulation (9,10). Both the ensuing hyperglycemia (9,10) and hyperinsulinemia (11) associated with glucose consumption have been implicated in the cognitive enhancement. Of importance to the type 2 diabetic population is the fact that glucose's effects are most consistently reported on behaviors mediated by the hippocampus and medial temporal lobes, including declarative memory (9,10). That is, long-term decrements in glucose regulation have been implicated in performance deficits associated with hippocampal functions, and it is precisely these same functions that benefit from acute glucose administration. An inverted U-shaped dose-response curve, however, is observed after acute glucose consumption in nondiabetic adults, and it has been suggested that a specific range of blood glucose concentration (8–10 mmol/l) is optimal for improved memory (12).

Whether benefits of glucose consumption extend to the type 2 diabetic population has not been tested. Therefore, the aim of this study was to examine the impact of carbohydrate consumption on cognitive performance in adults with type 2 diabetes. Rapidly absorbed sources of carbohydrate (bagel and white grape

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Abbreviations: MMSE, Mini-Mental State Examination.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

juice) were selected to eliminate the possibility that individuals with diabetes would find consumption of a glucose drink psychologically aversive and that this could impact cognitive function. Our previous studies in elderly nondiabetic individuals, however, suggest that the cognitive benefits of glucose consumption, either as a drink or in the form of carbohydrate foods (mashed potato or barley), do not differ from one another, at least over the first 2 h after consumption (8).

RESEARCH DESIGN AND METHODS

Test subjects

A total of 12 men and 10 women with type 2 diabetes were recruited at entry to an independent study involving chronic dietary changes and their impact on diabetes control. Exclusion criteria for the larger trial included HbA_{1c} >9.0%, insulin treatment, clinical and/or biochemical evidence of liver or kidney disease, thyroid dysfunction, or clinically significant neuropathy or gastroparesis. All subjects were treated with diet and/or oral hypoglycemic agents. To volunteer in the cognitive performance arm of the study, subjects had to demonstrate the absence of dementia (below age- and education-adjusted lower quartile on the Mini-Mental State Examination [MMSE]) (13,14). Three women only completed the first session and were eliminated from all analyses: two dropped out due to time constraints, and the third was eliminated due to use of neuroleptics to treat an underlying psychologic disorder. All procedures were approved by the Ethics Committees of St. Michael's Hospital and the University of Toronto, and participants signed separate consent sheets for this arm of the study.

Procedure

A repeated-measures, crossover design was used such that each subject served as his or her own control. All subjects were tested individually on two separate occasions after an overnight fast, with the order of food or placebo (water) randomly assigned. Subjects were tested at the same time of day (starting between 8:00 and 10:00 A.M.) at both sessions, separated by 2 weeks. Testing was completed within 2 weeks of the subjects' beginning the larger dietary intervention trial. The test food provided 50 g of available carbohydrate as one half plain white bagel (24 g carbohydrate) plus 160 ml white grape juice (26 g carbohydrate). Subjects were given 240 ml spring water on the placebo day for similarity of volumes ingested. The amount of carbohydrate provided matched the glucose load found to enhance memory in healthy elderly subjects (7–9,12, 15). For subjects using oral hypoglycemic agents, they were asked to bring their medications to the testing center. On days when food was provided, medication was taken 10–15 min before food consumption. On placebo days, food was provided after the test session and subjects were asked to take their medications at that time.

Declarative memory was assessed by paragraph and word list recall, each including both immediate and delayed (7 min) recall. Tests began at 15 and 23 min after the start of consumption (with delayed recall being assessed at 22 and 30 min, respectively). Half the subjects received the word list first and half received the paragraph first. This allowed for the comparison of word list/paragraph recall performance between subjects to determine whether the effect of carbohydrate consumption observed at 15 min was sustained over the half hour of testing. Subjects were distracted during the delay periods by completing the Trails Test Part B (paragraph) and the mood scale questionnaire (word list). Fasting venous blood was drawn at screening for the larger trial and analyzed for glucose, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, HbA_{1c}, creatinine, and urea in the routine clinical chemistry laboratory using standard methods for Kodak Ektachem analyzers (Eastman Kodak, Rochester, NY). During the cognitive testing periods, glucose was measured by finger prick (data shown) at the beginning (fasting; before taking any oral glycemic agent) of the session. Plasma glucose was estimated in these samples using a blood glucose meter (One Touch Basic Meter; Lifescan Canada, Mississauga, Canada).

Cognitive tests

Memory tests. Both the word list and paragraph recall used immediate and delayed (7 min) testing to distinguish between short- and longer-term memory processes. For the word list, four versions of a modified Rey Auditory-Verbal Learning Test (13) were developed, each consisting of 12 different nouns of similar difficulty (8). Subjects heard the same word list (one word per second) three times in succession and were asked to immediately recall as many words as possible. After a 7-min delay period, subjects were then asked to freely recall as many words as possible. The difference between the number of words recalled between the immediate (third presentation of list) and delay periods was calculated for each individual and is referred to as "words forgotten."

For paragraph recall, four paragraphs of comparable difficulty, length, and context, similar to the Logical Memory subtest of the Wechsler Memory Scale-Revised (WMS-R) (16) were used as described previously (8). After hearing the paragraph, subjects were immediately asked to recall as much of the story as they could. After a 7-min delay period, they were asked again to recall as much as they could from the paragraph. Each paragraph contained 25 pieces of information and a value of 1 was assigned to each piece of information (scoring unit) recalled. The difference between the number of scoring units recalled between the immediate and delay periods was calculated for each individual and is referred to as "scoring units forgotten."

Trails Test Part B. Four alternate versions of the standard Trails Test Part B Adult Form (or Trail-Making Test) (17) were used (original plus three new versions). This test measures speed for visual search, attention, mental flexibility, and motor function (13). Time to complete the test was used as a measure of performance.

Mood scale questionnaire. Subjective measures of mood were assessed using a visual analog scale (VAS) developed to detect changes in mood and subjective activation. The method yields two summary measures: global vigor (composite score of alert, sleepy, effort, and weary) and global affect (composite score of happy, calm, sad, and tense), each ranging in value from 0 to 100 (18).

Statistical analyses

Statistical analyses were conducted with SAS statistical software (version 6.12; SAS Institute, Cary, NC) using a repeated-measures ANOVA to determine the influence of food, time (testing at 15 or 22 min after consumption), delay (immediate versus delayed recall), repeat (three pre-

Table 1—*Subject characteristics and baseline cognitive performance*

	Women (n = 7)	Men (n = 12)
Age (years)	64 ± 13	62 ± 7
Height (cm)	156 ± 9	173 ± 8*
Weight (kg)	69.8 ± 19.3	73.3 ± 13.5
BMI (kg/m^2)	29.3 ± 6.3	24.5 ± 2.3*
Triacylglycerides (mmol/l)	1.91 ± 1.25	1.58 ± 1.53
Total cholesterol (mmol/l)	5.67 ± 0.51	4.95 ± 1.15
HDL cholesterol (mmol/l)	1.16 ± 0.15	1.05 ± 0.28
LDL cholesterol (mmol/l)	3.63 ± 0.89	3.19 ± 0.90
Blood pressure (mmHg)	134/76 ± 14/10	132/79 ± 17/10
Urea (mmol/l)	5.4 ± 0.67	5.8 ± 1.7
Creatinine (μmol/l)	69.3 ± 15.0	91.0 ± 20.6
Fasting glucose (mmol/l)	8.22 ± 1.47	7.68 ± 1.46
HbA_{1c}	0.072 ± 0.022	0.078 ± 0.010
MMSE†	28.5 ± 1.4	29.3 ± 0.8
Paragraph recall — immediate (no. scoring units)‡	8.5 ± 3.6	8.5 ± 3.6
Paragraph recall — delayed (no. scoring units)	8.0 ± 3.7	7.9 ± 3.7
Word list — first presentation (no. words)§	4.0 ± 1.4	4.2 ± 1.6
Word list — second presentation (no. words)	5.7 ± 2.1	6.0 ± 1.7
Word list — third presentation (no. words)	7.0 ± 2.2	8.2 ± 2.2
Word list — delayed recall (no. words)	5.3 ± 2.9	6.3 ± 2.1

Data are means ± SD. *Significant difference between sexes ($P < 0.05$); †MMSE scores out of 30; ‡each paragraph contained 25 pieces of information and subjects were assigned a value of 1 for each piece of information (scoring unit) recalled; §each word list contained 12 unrelated nouns and subjects were assigned a value of 1 for each word correctly recalled.

sentations of word lists), and their interactions. The relationship between baseline (placebo) cognitive performance and various health characteristics was assessed by multiple regression analyses using performance under the placebo condition as the response variable and all measured blood values, age, BMI, MMSE score, and subjective measures of global affect and vigor as predictor variables. Variance inflation factors were examined to determine interrelationships among the predictor variables.

RESULTS

Subject characteristics

There was no difference between sexes on the basis of age, blood lipid profile, blood pressure, urea, creatinine, fasting venous glucose, HbA_{1c}, or cognitive function as assessed by the MMSE. However, women had a greater mean BMI than men (Table 1).

Baseline cognitive performance

Multiple stepwise regression analyses were used to determine which subject characteristics predicted cognitive performance under placebo conditions. The data for fasting plasma glucose on the day of cognitive testing, rather than that obtained during screening, were used. Whereas all subject characteristics listed in Table 1 and subjective measures of global vigor and affect were entered into the model, only HbA_{1c} levels were associated with paragraph recall under both the immediate ($R^2 = 0.30$, $P = 0.024$; Fig. 1) and delayed ($R^2 = 0.22$, $P = 0.055$; data not shown) conditions. Individuals with better overall glycemic control demonstrated better paragraph recall. To ensure that the individual with the lowest HbA_{1c} did not drive this association, this value was reserved and the analyses were rerun. For immediate recall, the association weakened ($R^2 = 0.21$, $P = 0.082$), but a trend was still apparent; nevertheless, it was absent for the delayed recall.

In contrast to the paragraph recall, fasting glucose (partial $R^2 = 0.09$, $P = 0.102$), rather than HbA_{1c} levels, was weakly associated with the number of words recalled after the first presentation of the word list (see Fig. 1 for linear regression). In addition to plasma glucose, global vigor (partial $R^2 = 0.27$, $P = 0.031$), systolic blood pressure (partial $R^2 = 0.16$, $P = 0.070$), and MMSE score (partial $R^2 = 0.12$, $P = 0.079$) were also predictive of word recall. The only predic-

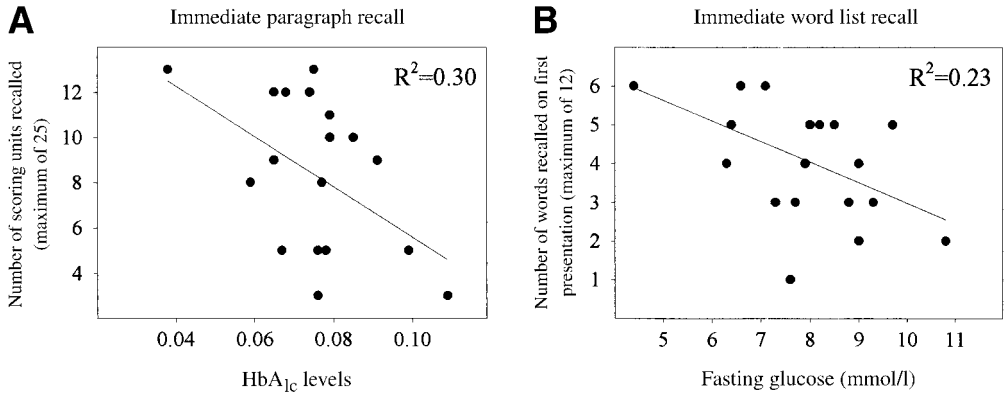

Figure 1—*Linear regression between measures of glucose regulation and declarative memory in adults with type 2 diabetes. Fasting HbA_{1c} values were obtained during screening, whereas fasting glucose was measured on the day of cognitive testing. Fasting HbA_{1c} was the only variable measured that predicted performance on immediate (A) and delayed (not shown) paragraph recall. Whereas fasting glucose levels were related to word list recall on the first hearing of the word list (B) and the number of words forgotten over the delay period (not shown), multiple regression analyses showed that it was not the only predictive variable (see text).*

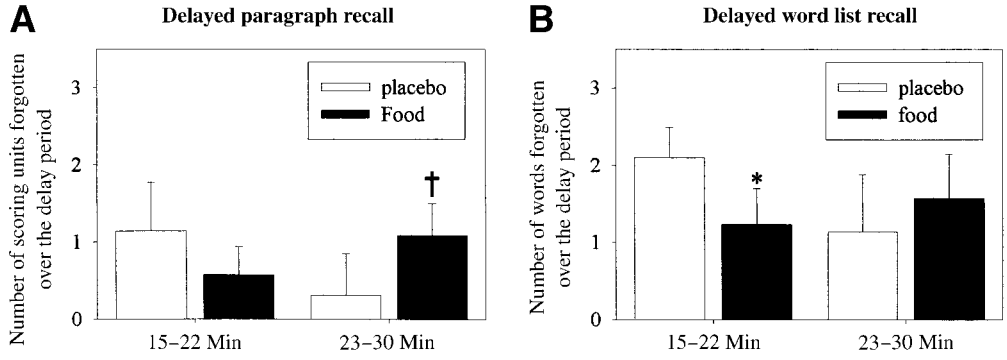

Figure 2—*Carbohydrate ingestion influenced delayed paragraph* (A) *(time × delay:* P = *0.044) and word list* (B) *(time × delay:* P = *0.046) recall in a time-dependent fashion. Data represent the mean number of scoring units (paragraph recall) or words (word list recall) forgotten over the 7-min delay period. A total of 50% of the subjects were tested on paragraph recall at 15 min and word list recall at 22 min, and 50% of the subjects received the paragraph recall at 22 min and the word list recall at 15 min. Consumption of 50 g of available carbohydrate as one half bagel and white grape juice impaired paragraph recall performance when testing was commenced 23 min after consumption (†*P = *0.096). By contrast, enhanced word list recall was observed in individuals who started the word list recall testing at 15 min after consumption (**P = *0.051).*

tors of the number of words recalled after the 7-min delay were MMSE score (partial $R^2 = 0.44$, $P = 0.004$), global vigor (partial $R^2 = 0.14$, $P = 0.053$), BMI (partial $R^2 = 0.14$, $P = 0.029$), and age (partial $R^2 = 0.08$, $P = 0.056$). A variance inflation factor of 1.41 was apparent for age, presumably reflecting the interrelationships among age, MMSE score, and BMI. However, fasting glucose (partial $R^2 = 0.09$, $P = 0.148$) weakly predicted the number of words forgotten over the delay period. Systolic blood pressure was negatively associated with the number of words forgotten (partial $R^2 = 0.29$, $P = 0.027$) while Hb levels demonstrated a positive relationship (partial $R^2 = 0.15$, $P = 0.078$). Although a vast number of characteristics were associated with word list recall scores, fasting glucose tended to be negatively associated with recall score on the first presentation of the word list and the ability to remember words over the 7-min delay, again suggesting that individuals in better glycemic control demonstrated better verbal recall.

Effect of carbohydrate consumption on declarative memory performance

Immediate paragraph recall was not influenced by food ingestion ($P = 0.395$). Instead, carbohydrate intake impacted the amount of information (scoring units) forgotten over the delay period (Fig. 2). This effect interacted with time of testing (food × time; $P = 0.055$). No impact of carbohydrate consumption was observed when testing was commenced at 15 min after consumption ($P = 0.280$). By contrast, impaired performance after carbohydrate consumption was observed in individuals who started the paragraph recall testing at 22 min after consumption ($P = 0.096$).

No effect of food intake was observed on immediate recall of the word list, or its learning, over the three presentation trials ($P = 0.383$). Instead, the impact of carbohydrate consumption was associated with delayed recall, or the number of words forgotten over the delay period. Once again, this effect interacted with the time of testing (food × time; $P = 0.058$). Carbohydrate consumption enhanced memory performance when testing was commenced 15 min after consumption ($P = 0.051$) but had no impact on performance in individuals who started the testing at 22 min after consumption ($P = 0.408$).

Trails testing and subjective mood

No effect of food consumption was observed on the Trails Test Part B ($P = 0.410$; 105 ± 34 and 120 ± 48 s after water and food, respectively). Subjectively rated global vigor ($P = 0.381$) and global affect ($P = 0.909$) did not change over the 30 min of testing (not shown) and was unaffected by food consumption (vigor: $P = 0.559$, 62 ± 24 and 66 ± 24 cm for water and food, respectively; affect: $P = 0.588$, 75 ± 18 and 70 ± 25 cm for water and food, respectively).

CONCLUSIONS — This study examined the association between glycemic control and cognitive performance under fasting conditions and the impact of acute carbohydrate consumption on cognitive function in adults with type 2 diabetes. The results demonstrate a negative relationship between measures of glycemic control, specifically HbA_{1c} and fasting glucose, and fasting cognitive performance such that individuals in poorer glycemic control show poorer performance on tests of verbal recall. Although memory improvement was observed immediately after carbohydrate consumption, similar to that observed in healthy older adults, this was followed by impairment in performance.

The associations observed between fasting cognitive performance and measures of glucoregulatory status in study participants is consistent with a direct impact of type 2 diabetes on central nervous system functioning. Similar associations between HbA_{1c} and cognitive functions have been observed by some but not others (2). Problematic to understanding this relationship is the fact that other complications typically observed with type 2 diabetes, including cardiovascular disease, hypertension, and depression, are also associated with cognitive deficits. Consequently, the presence of type 2 diabetes may be a proxy indicator of predisposition to these other disorders (1,2). In this study, blood lipid profile was not associated with any of the cognitive measures and low, not higher, systolic blood pressure was predictive of poorer performance on the word list recall. Finally, whereas clinical diagnostic tests were not used to assess depression, a subjective measure of global affect did not predict performance, but greater subjective mea-

sures of global vigor were associated with better word list but not paragraph recall performance. By contrast, measures of glucoregulation associated with both tests of verbal recall and HbA_{1c} were the only predictors of paragraph recall score. Consistent associations between the paragraph and word list tests were observed with the immediate recall, whereas different measures of delayed recall (absolute score for paragraph and number of words forgotten over the delay period for the word list) demonstrated significant associations, suggesting that both components of these tests were sensitive to differences in glycemic control. Although duration of diabetes was not assessed in this study, these results support the argument that some aspect of diabetes per se does relate to cognitive function in this population (19). Nevertheless, it is recognized that concurrent blood measures are not indicative of potential pathophysiologic events occurring historically and that subjective measures of global affect are not sufficient to diagnose depression clinically, making it impossible to rule out the contribution of these factors (20).

The specific mechanism linking type 2 diabetes with cognitive deficits has not been identified; however, extraneuronal hyperglycemia, disturbed brain glucose metabolism, altered brain insulin signaling (1,21), and complications secondary to potential hypercortisolemia (22) have all been implicated. Beyond factors that may contribute to cognitive deficits under baseline conditions, these data also demonstrate that consumption of rapidly absorbed carbohydrate foods, providing only 50 g of available carbohydrate, can produce further decrements in memory function. Consistent with other studies examining glucose-induced changes in cognition (9,10), no effect of food consumption was observed on the immediate recall components of the paragraph and word list tests, Trails Test scores, or subjective measures of mood, suggesting a specific effect on delayed recall performance. What differentiates the individual with diabetes is that this improvement on delayed recall is not sustained over the course of testing, as observed in healthy older adults (8). Testing during the first 15 min after consumption demonstrated improvements in longer term memory on word list performance and a trend toward benefits on paragraph recall ($P = 0.28$). This early stimulation in memory function may be secondary to either the initial rise in blood glucose after carbohydrate consumption, secondary to release of gut peptides, or associated with medication use. Many argue that the cognitive enhancing capabilities of glucose are mediated via changes in central nervous system metabolism that could include enhanced production of acetylcholine and/or γ-aminobutyric acid (9,10). One possibility is that adults with type 2 diabetes remain sensitive to this positive effect of glucose during the immediate postprandial period. Alternatively, stimulation of the brain-gut axis has been associated with cognitive enhancement (23), with a variety of gut peptides implicated (24), suggesting that this axis remains intact in the type 2 diabetes population and that the benefits observed relate to a nonspecific effect of energy ingestion (15). Finally, hypoglycemic medications such as glibenclamide, which block ATP-sensitive potassium channels, result in cognitive benefits in rodents when injected intracerebrally (25), supporting an argument that the cognitive enhancements observed during the early testing period was secondary to subjects consuming their medications.

More important, however, is the deficit observed at the later testing period. The degree to which this is associated with postprandial hyperglycemia and/or hyperinsulinemia is unknown. Previous research in healthy adults indicated an inverted U-shaped dose-response curve after acute glucose consumption, such that higher doses of blood glucose result in cognitive deficits (12). Adults with type 2 diabetes may simply be more likely to experience those levels of hyperglycemia that have been previously associated with cognitive deficits. Results from this study would support such an argument. Whereas many studies of diabetes have attempted to link frequency of hyper- and/or hypoglycemic episodes to cognitive impairments, few have examined cognitive function during actual hyperglycemic periods. Using hypoglycemic and hyperglycemic clamp techniques, adults (26,27) and adolescents (28) with type 1 diabetes showed profound deficits during hypoglycemia on complex, but not simple, tasks. Nevertheless, the detrimental effect of hyperglycemia only trended toward statistical significance. One possibility is that once steady-state hyperglycemic conditions have been attained (such as those obtained with clamp techniques), cognitive deficits associated with rising blood glucose levels are no longer apparent. Alternatively, because brain metabolic disturbances and glucose transporter characteristics can differ in type 1 and type 2 diabetes (29), the different cognitive responses to hyperglycemia may reflect inherent differences in these two disease states.

In summary, results from this study demonstrate that the degree of glycemic control is related to cognitive performance in adults with type 2 diabetes. Additionally, consumption of rapidly absorbed carbohydrate foods, providing as little as 50 g of available carbohydrate, can produce memory deficits. Whereas postprandial hyperglycemia and/or hyperinsulinemia may be associated with these deficits, further research is required to uncover the metabolic events leading to cognitive impairment.

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