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Adaptation in brain glucose uptake following recurrent hypoglycemia

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ABSTRACT **Brain glucose metabolism is impaired during hypoglycemia, but, if sustained, brain metabolism reverts to normal in animal models—data in man are lacking. We tested the hypothesis that adaptations occur to allow maintenance of normal rates of brain glucose uptake (BGU) following recurrent hypoglycemia in man. Twelve normal humans were studied over 4 days. On the initial day, arterial plasma glucose concentrations were decreased from 4.72 to 2.50 mmol/liter in five 0.56 mmol/liter steps. Cerebral blood flow, brain arteriovenous glucose difference, BGU, and cognitive function were quantitated at each step. BGU was initially impaired at the 3.61 mmol/liter glucose step ($P = 0.04$) and was antedated by increments in epinephrine that began at 4.16 mmol/liter ($P = 0.03$). The onset of hypoglycemic symptoms occurred during the 3.61 mmol/liter glucose step ($P = 0.02$), whereas tests of cognitive function generally deteriorated at the 3.05 mmol/liter step ($P < 0.05$). During the next 56 hr, mean glucose concentrations were kept at 2.9 ± 0.1 mmol/liter and reached normal only during meals. The stepped clamp protocol was repeated beginning at 4.16 mmol/liter on the last day. No decrement in BGU was observed at any step; cognitive function was preserved until significantly lower glucose concentrations on the final day relative to the first ($P = 0.04$). Subjects remained asymptomatic of hypoglycemia until they reached a glucose concentration of 2.50 mmol/liter ($P < 0.001$ vs. day 1), while initial increments in all counterregulatory hormones were forestalled to lower glucose steps than on day 1. Therefore, adaptations occur that allow normal BGU and cerebral function to be maintained during recurrent systemic hypoglycemia. Counterregulatory events that should result in symptoms of hypoglycemia and increments in endogenous glucose production are prevented until extremely subnormal glucose concentrations.**

Under normal circumstances, glucose is the only fuel neuronal tissue can use for energy (1). The brain can neither synthesize nor store more than a few minutes' worth of glucose; thus a continuous systemic supply is essential for normal cerebral metabolism (2). Glucose arrives in the central nervous system (CNS) through the specific brain capillary endothelial transporter, GLUT 1 (3), at a rate that is generally far in excess of the phosphorylation rate by hexokinase (2). Therefore, at euglycemia, glucose transport is not rate-limiting for brain metabolism; but during an acute reduction in the glucose concentration, a level is reached where transport assumes a rate-limiting role. Beyond this critical point, hexokinase is not fully saturated and brain energy metabolism deteriorates. Among the ultimate consequences of neuroglycopenia are initial elevations in epinephrine and glucagon, which serve to increase systemic glucose production and restore glucose provision to the brain. Widespread regions of the brain have been shown to direct this hormonal response during acute CNS fuel deprivation (4). Maintaining cerebral normoglycemia while inducing systemic hypoglycemia greatly attenuates this counterregulatory hormone response (4, 5).

Chronic changes in the antecedent level of glycemia (either sustained hyperglycemia or hypoglycemia) induce alterations in brain glucose metabolism in rodents. Chronically hyperglycemic animals experience low fractional extraction (and presumably reduced transport capacity), while animals with diabetes treated to reduce their glucose levels toward normal have relatively higher fractional rates of glucose extraction (6). Based on the preceding series of facts, we presume that in sustained human hypoglycemia, normal increments in epinephrine and glucagon will fail to occur, reflecting a normalization of glucose availability to the brain secondary to improved glucose uptake.

We tested the hypothesis that the systemic glucose concentration required to impair brain glucose uptake (BGU) would occur near the usual basal glucose concentration in nondiabetic subjects but that after 56 hr of interprandial hypoglycemia, BGU would remain normal even at very subbasal glucose levels. Further, we hypothesized that increments in counterregulatory hormones, symptoms of hypoglycemia, and impairment in cognitive functions tests would be delayed until critically low arterial glucose levels were reached after the period of interprandial hypoglycemia.

METHODS

Subjects. Twelve normal volunteers (seven men and five women) ranging in age from 21 to 42 years (mean ± SD, 28.4 ± 7.9 years) gave their informed consent to participate in investigations approved by the Human Research Review Committee at the University of New Mexico. None was taking any medication, and all had normal screening laboratory chemistry.

Protocol. Investigations were conducted in the General Clinical Research Center at the University of New Mexico. A flexible cannula was introduced retrograde into the right internal jugular vein and advanced until resistance was met. In agreement with others using this placement technique (7), our prior investigations uniformly demonstrated correct placement of the cannula tip at the jugular bulb by roentgenogram (8); therefore x-ray confirmation was not used in these studies. Radial arterial and antecubital intravenous cannulas were introduced for sampling and infusions, respectively.

Regular human insulin, 12.0 pmol/kg per min, was infused continuously with variable-rate 20% dextrose to generate a starting glucose concentration of 4.72 mmol/liter by 0800 hr. Arterial plasma glucose concentration was determined every

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Abbreviations: BGU, brain glucose uptake; CBF, cerebral blood flow; $(A - V)_{glu}$, arteriovenous glucose difference; CNS, central nervous system; NS, not significant.

5–7 min to guide dextrose adjustments. Arterial glucose was decreased by 0.56 mmol/liter (10 mg/dl) every 60–80 min to produce five glycemic plateaus between 4.72 and 2.50 mmol/liter. After 20 min when brain glucose concentration was allowed to come into equilibrium with the systemic glucose concentration, BGU was determined after the technique of Kety and Schmidt (9) utilizing N_2O as the tracer gas as described (8). Subjects then scored 12 symptoms of hypoglycemia from 0, not at all, to 7, most intense. Symptoms were subclassified into autonomic (nervous, tingling, shaky, sweating, heart pounding, hungry) and neuroglycopenic (tired, dizzy, faint, blurred vision, difficulty thinking) (10). Motor and cognitive function tests were performed as follows: immediate recall and delayed recall of 12-item word lists (11), finger tapping speed (12), and the Stroop color word test (13). The sum of three successive trials of immediate recall (maximum score = 36) is reported, while delayed recall has a maximum score of 12. Five different word lists were utilized in random sequence between patients to minimize learning and sequence effects. Psychomotor function (finger tapping) is reported as the mean of five 10-sec trials for each hand. The Stroop test score was the sum of correct responses across three 45-sec conditions: reading words, naming colors, and naming the color of ink in which an incongruous color name was written (e.g., saying "red," when the word "blue" was printed in red ink). Subjects were familiarized with these tests prior to the first day. Glucose concentration was then decreased over 20 min to the next glycemic step with careful attention to avoid overshooting the target. The sequence of equilibration, determination of rate of BGU, and cognitive function testing was repeated at each plateau.

Arterial and jugular venous samples for glucose were collected at the beginning, middle, and end of each cerebral blood flow (CBF) determination. Glucose concentration was quantitated by the glucose oxidase technique (Beckman), with each sample determined four or five times to yield coefficients of variation of 0.5%. The reported arteriovenous glucose difference [$(A - V)_{glu}$] is the mean of the three glucose differences. Arterial blood for insulin, growth hormone, glucagon, cortisol, and pancreatic polypeptide was collected at the beginning and end of each blood flow measurement. Blood for catecholamines was collected at the end of each CBF measurement.

During the next 56 hr, glucose concentration was monitored every 30–45 min by Beckman analyzer with a target arterial glucose of 3.0 mmol/liter. The arterial cannula was removed for safety reasons after the first 24 hr of study and the jugular venous glucose concentration was maintained near 2.8 mmol/liter [at this level of glycemia, the usual $(A - V)_{glu}$ is 0.3–0.4 mmol/liter]. Insulin requirements to achieve this level of glycemia decreased progressively over the 56 hr. The mean glucose concentration (including postprandial periods) was 2.9 ± 0.1 mmol/liter for this 56 hr.

At 0400 hr on the last day, the internal jugular glucose concentration was raised to 4.16 mmol/liter and maintained there until after a radial arterial cannula was introduced at 0700 hr. The 12.0 pmol/kg per min insulin infusion was started again and the arterial glucose concentration was maintained at 4.16 mmol/liter. This lower starting point for the last day was selected based on our prior observation that BGU is not different between the 4.72 and 4.16 mmol/liter (14). Potassium was infused at 3 meq/hr through all 4 days.

Analytical Methods. Plasma insulin (15), cortisol (16), glucagon (17), growth hormone (18), and pancreatic polypeptide (19) were measured by radioimmunoassay. Epinephrine and norepinephrine were measured by single isotope radioenzymatic technique (20). Analyses for N_2O content were made with a N_2O trace infrared spectrophotometer (Traverse Medical Monitors, Saline, MI) after the method of Robertson *et al.* (21).

Calculations and Statistical Methods. BGU is the product of the $(A - V)_{glu}$ and CBF. Differences in parameters, day 1 vs. day 4, were evaluated by repeated measures analysis of variance (22). Once significance was established, pair-wise comparisons between each day's baseline and values at subsequent glycemic steps were made utilizing two-tailed, paired *t* tests. The highest common glycemic step, 4.16 mmol/liter, served as the reference baseline for each day. When data distribution for a given parameter were not normal, nonparametric Wilcoxon signed rank tests were employed. *P* values <0.05 were considered statistically significant and *P* = NS denotes "not significant." Data in figures represent the mean ± 1 SE, unless otherwise noted.

RESULTS

Mean Arterial Glucose Concentration During Stepped Clamps. Glucose decreased as desired on both days. Mean glucose concentrations were comparable on days 1 and 4 (*P* = NS) (Fig. 1). Due to variability in time required to achieve a stable plateau glucose concentration, data between plateaus are not shown.

Arterial Insulin Concentrations During Stepped Clamp Studies. Mean insulin concentrations ranged between 1028 ± 124 pmol/liter and 1297 ± 119 pmol/liter on day 1 (*P* = NS). On day 4, concentrations were slightly (but not significantly) lower, ranging between 887 ± 64 pmol/liter and 1177 ± 73 pmol/liter (*P* = NS).

$(A - V)_{glu}$, CBF, and Rate of BGU. No decrease in any parameter of this section was noted between the 4.72 and 4.16 mmol/liter steps on day 1 (Fig. 2). Relative to the common baseline of 4.16 mmol/liter, the first significant decrease in the $(A - V)_{glu}$ occurred at the 3.61 mmol/liter step on day 1 (*P* = 0.039), but not until the 2.50 mmol/liter step on the final day (*P* = 0.006, *P* < 0.001, day 1 vs. day 4). The cross brain $(A - V)_{glu}$ decreased at lower glucose levels on day 4 vs. day 1 (*P* = 0.02). Baseline $(A - V)_{glu}$ at the 4.16 mmol/liter step was substantially lower on day 4, 0.6 ± 0.03 mmol/liter vs. 0.5 ± 0.04 mmol/liter (*P* = 0.04). No significant change in CBF was observed on either day independently. Flow was higher after intermittent hypoglycemia (*P* = 0.03, day 1 vs. day 4). BGU first fell as the glucose concentration fell from 4.16 to 3.61 mmol/liter on day 1 (*P* = 0.034). No quantitative differences were observed between baseline studies done at 4.72 mmol/liter on day 1 and rates observed at any glycemic level on day 4.

Catecholamine Responses to Hypoglycemia and Autonomic and Neuroglycopenic Symptom Scores. Mean epinephrine concentration rose from 310 ± 30 to 630 ± 100 pmol/liter as glucose fell from 4.72 to 4.16 mmol/liter on day 1 (*P* < 0.006) (Fig. 3). Epinephrine concentration at the 4.16 mmol/liter

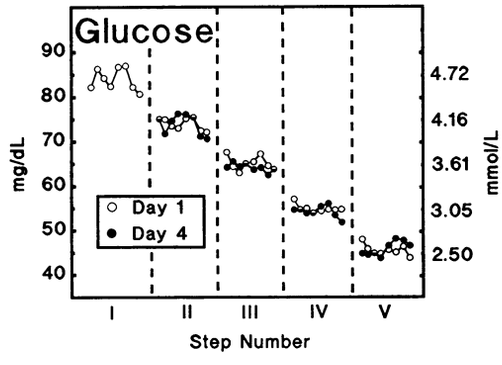

FIG. 1. Mean (±SE) arterial glucose concentration on day 1 and after 56 hr of intermittent hypoglycemia, day 4. Achieved glucose concentrations at each glycemic step were not different between days of study.

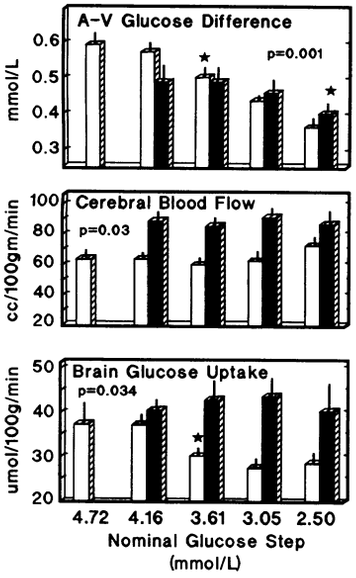

FIG. 2. Mean (±SE) $(A - V)_{glu}$, CBF, and rate of BGU. Open bars, day 1; closed bars, day 4. No differences were noted for any parameter as glucose decreased from 4.72 and 4.16 mmol/liter on the day 1. The first significant difference from 4.16 mmol/liter is denoted by * ($P < 0.04$). The significance between day 1 vs. day 4 is presented as P values from repeated measures ANOVA.

step was higher on day 1 vs. day 4 (630 ± 102.1 vs. 340 ± 60 pmol/liter, $P = 0.03$). On day 4, no rise in epinephrine was observed until the 2.50 mmol/liter step ($P < 0.001$, day 1 vs. day 4). Norepinephrine increased at 3.05 mmol/liter on day 1 ($P = 0.02$) and 2.50 mmol/liter on day 4 ($P = 0.02$) (day 1 vs. day 4, $P = 0.0045$). Autonomic symptoms increased at 3.61 mmol/liter on day 1 ($P = 0.03$) and slightly, but significantly, increased at 3.05 mmol/liter on day 4 (from 1.0 ± 0.5 to 1.9 ± 0.6, $P = 0.02$). Individual analysis of scores for sweating demonstrated a rise at 3.05 mmol/liter on day 1 ($0.01 < P < 0.05$), but no rise was seen on day 4 ($P = 0.10$). Neuroglycopenic symptoms increased at 3.05 mmol/liter on day 1 ($P < 0.001$), but not until 2.50 mmol/liter on day 4 ($P = 0.006$) ($P = 0.02$, day 1 vs. day 4).

Glucagon, Growth Hormone, Cortisol, and Pancreatic Polypeptide. On day 1, initial increments over baseline for each hormone occurred at the 3.61 mmol/liter step ($P = 0.01, 0.03, 0.005, 0.04$, respectively) (Fig. 4). Each of these factors rose only at the final 2.50 mmol/liter glycemic step on day 4 (day 1 vs. day 4, $P = 0.03$). More robust glucagon secretion was likely suppressed by hyperinsulinemia.

Cognitive Function Testing. Memory tests were impaired at the final glucose step on both days (P = NS) (Table 1). Stroop scores fell at 3.05 mmol/liter on day 1, but not until 2.50 mmol/liter on day 4 ($P = 0.04$, day 1 vs. day 4). Finger tapping was impaired at 3.05 mmol/liter on day 1, but remained normal even at 2.50 mmol/liter on the final day ($P = 0.004$, day 1 vs. day 4). Twelve additional subjects underwent testing without hypoglycemia on any day to assess learning. As during the experiment, control scores for tests tended to be higher at the start of day 4 but were stable or increased at equivalent rates over each of the days. Thus, although learning occurred, comparison of experimental days is justified.

DISCUSSION

The current investigations demonstrate that impairment in BGU occurs as the systemic glucose concentration falls to 3.61 mmol/liter during an acute episode of hypoglycemia. This threshold occurs coincident with the systemic glucose concentration previously known to be insufficient to maintain normal levels of neuronal glucose-6-phosphate in rats (23). However, after 56 hr of interprandial hypoglycemia, BGU is maintained at normal rates even at the final glucose concentration studied, 2.50 mmol/liter. As a consequence, at glucose concentrations classically associated with hypoglycemia, no efferent neural signal is generated to drive normal counterregulatory hormone responses. Thus, normal increments in counterregulatory hormones are forestalled to lower glucose concentrations following recurrent hypoglycemia. Consistent with prior investigations, we found no change in CBF during the initial episode of hypoglycemia; however, by the final day of investigation, basal CBF had increased significantly, but remained constant throughout that final day of study. Many factors may have contributed to our observed improvement in BGU.

The magnitude of the change in extraction of glucose from the circulation into the brain, E, can be estimated from the following exponential function (24):

$$E = 1 - e^{-PS/F}.$$

The permeability surface area product, PS, encompasses the total quantity of glucose transporters and their activity and has been noted to increase by 40% in chronically hypoglycemic rats (25). Glucose deprivation of cultured bovine brain endothelial cells leads to stabilization of mRNA for GLUT 1 and a rise in transcript abundance (26) as well as a 60% increase in transporter expression within 50 hr (27). Thus, McCall's original observation of an increased rate of brain glucose extraction during hypoglycemia in animals with insulinoma must be at least partially explained by increased GLUT 1 (6). Significant increments in flow, F in the above equation, occurred in our study and also augment BGU.

While some investigations have observed increased CBF at glucose concentrations of <2.2 mmol/liter (28–31), acute decrements in glucose concentration to 3.0 mmol/liter have not proven sufficient to increase flow (32). Utilizing $^{11}CH_3F$

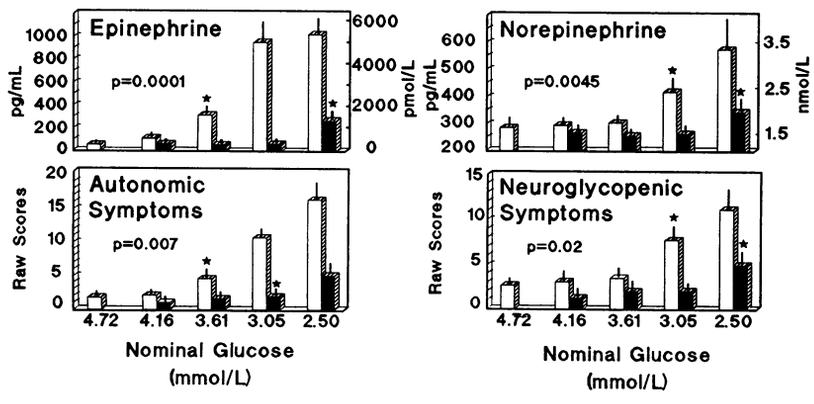

FIG. 3. Mean (±SE) epinephrine, norepinephrine, and autonomic and neuroglycopenic symptoms of hypoglycemia. Open bars represent data from the initial day of study and closed bars represent data after 56 hr of intermittent hypoglycemia. The first significant difference from the 4.16 mmol/liter step is denoted by *, $P < 0.03$.

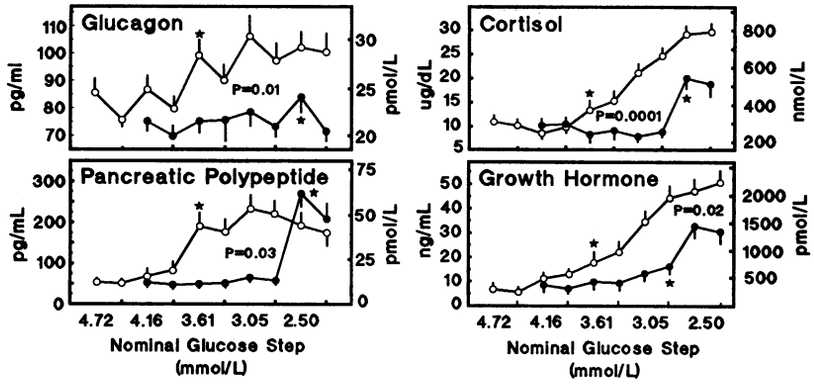

FIG. 4. Mean (±SE) glucagon, pancreatic polypeptide, cortisol, and growth hormone levels. ○, First day of investigation; ●, stepped clamp investigation after 56 hr of hypoglycemia. The first values different from the 4.16 mmol/liter step are denoted by *, $P < 0.01$.

positron emission tomography (PET), Grill *et al.* (33) observed a 30% increase in CBF in eight euglycemic patients with insulin-dependent diabetes with mean hemoglobin A_{1c} of 6.9% and prior episodes of hypoglycemia unawareness. The significance of any increase in flow with regard to glucose flux depends upon whether it is linear or occurs through expansion of total capillary volume. Unidirectional flux of glucose, J, is the product of glucose extraction, the arterial glucose concentration, c_a, and the cerebral flow, F (24):

$$J = (1 - e^{-PS/F}) \cdot c_a \cdot F.$$

If PS is stable and linear flow through a fixed capillary volume, F, is doubled, then unidirectional flux of glucose will only increase ≈8%. On the other hand, if PS increases by 20%, as Pelligrino observed during chronic hypoglycemia in rats (25), and total blood flow increases 30% as we report, then the overall flux of glucose would be increased by 20%. This benefit almost completely offsets the 25% reduction in BGU induced on day 1 of our investigations as systemic glucose concentration fell from normal to 2.50 mmol/liter. The concept of capillary recruitment remains controversial as a contributor to enhanced transport; however, it has been documented during periods of hypoglycemia in neonates (34). The N_2O equilibrium technique we employed to measure flow cannot differentiate increased linear flow from increased capillary volume.

The limited available data in man in the field of quantitative brain glucose kinetics during hypoglycemia deserve review. Brooks *et al.* (35), using fluorodeoxyglucose and PET, were unable to demonstrate alterations in estimates of unidirectional flux in five patients with diabetes studied at normoglycemia. The wide range of glycemic control of these patients likely allowed inclusion of some with recent hyperglycemia, thus no adaptation would have been expected. Gutniak *et al.* (36) used PET to study well-controlled patients with insulin-dependent diabetes and nondiabetics. As the arterial glucose fell from 6.0 mmol/liter to 2.5 mmol/liter, the patients experienced a smaller percent reduction in brain glucose metabolism than nondiabetics, 28% vs. 40%, respectively. Estimates of unidirectional flux of glucose were not different between the groups. However, overall basal rates of glucose metabolism yielded from this technique were 25–50% below well-established norms, thus raising questions regarding the quantitative reliability of the measurements.

Key to our findings is how validly the internal jugular glucose concentration reflects cerebral venous drainage. Only 2.7% of internal jugular blood is derived from the external carotid circulation (37). Venous drainage from the eye, supplied by a branch of the internal carotid artery, has not been quantitated. Based on the velocity of ophthalmic arterial flow (38) and the mass of tissue to be perfused relative to cortex, the contribution probably represents a minority (1%) of internal jugular drainage. With the methods we employ, an $(A - V)_{glu}$ of 0.1 mmol/liter (1.8 mg/dl) can be determined with 90% power if 12 subjects are studied. Therefore, potentially significant decrements in the $(A - V)_{glu}$ may be overlooked by our method [e.g., possible reductions in the $(A - V)_{glu}$ between the 4.72 and 4.16 mmol/liter on the day 1].

Attenuation in responses from both limbs of the autonomic nervous system was evident during our study. The glucose concentration required to cause epinephrine secretion (mediated by CNS sympathetic outflow) (4, 5), pancreatic polypeptide release (from vagally innervated PP cells in the pancreas) (39), and sweating (a postganglionic cholinergic event) (40) decreased from day 1 to day 4. Because many of the fundamental warning signs of incipient hypoglycemia (shakiness, heart pounding, nervousness, and sweating) are triggered by autonomic nervous system activation, subjects were dependent on neuroglycopenic symptoms to identify hypoglycemia. Yet, the onset of neuroglycopenia (both symptoms and cognitive dysfunction) was forestalled to 2.50 mmol/liter on the final day. Thus, awareness of hypoglycemia was obscured.

Consistent with normalization of BGU during hypoglycemia, we found that most tests of higher cortical function were preserved at lower glucose concentrations after hypoglyce-

Table 1. Cognitive function studies

Test	Glucose, mmol/liter			
	4.16	3.61	3.05	2.50
		Day 1		
Immediate recall	25.8 ± 1.4	26.3 ± 1.2	26.1 ± 1.9	20.4 ± 1.8*
Delayed recall	9.9 ± 0.6	8.6 ± 0.7	8.8 ± 1.0	6.0 ± 1.2*
Stroop	227.3 ± 8.6	226.5 ± 11.2	204.2 ± 12.9*	167.4 ± 16.6
Finger tapping	73.7 ± 2.4	71.4 ± 2.3	64.9 ± 5.1*	54.7 ± 7.5
		Day 4		
Immediate recall	30.1 ± 1.0	28.4 ± 1.4	27.7 ± 2.2	22.4 ± 1.8*
Delayed recall	10.6 ± 0.5	10.2 ± 0.9	9.9 ± 1.0	6.9 ± 1.6*
Stroop	246.8 ± 7.7	243.8 ± 5.7	236.6 ± 10.2	158.3 ± 23.0*
Finger tapping	65.9 ± 3.3	67.7 ± 3.0	71.4 ± 2.2	67.7 ± 3.0

*First value different from baseline of 4.16 mmol/liter, $P \leq 0.05$.

mia. The Stroop test requires complex activation and inhibition of numerous cortical regions (41). When considered together with the regions required to perform finger tapping, the majority of brain tissues must increase their ability to maintain normal glucose uptake after recurrent hypoglycemia. Memory was unaffected in our investigation but uniquely involves the hippocampus, which has a high metabolic rate at euglycemia and may be unable to augment glucose uptake to the extent of other tissues (42). Our findings complement observations in patients with insulinoma whose cognitive function is impaired only at low levels of glycemia, but who revert to normal after tumor resection (43).

The landmark findings of the Diabetes Control and Complications Trial have now substantiated that improved glycemic control will prevent or forestall chronic complications in patients with diabetes (44). Yet the limiting factor for achieving near-normal glycemic control continues to be the increased risk of severe hypoglycemia associated with intensified management. Sixty percent of these severe episodes occurred without warning (45). Speculation that an adaptation in the CNS might exist in patients with diabetes, depending upon antecedent glycemia, appeared nearly a decade ago (46). Amiel *et al.* (47) observed that lower glucose concentrations were required to initiate epinephrine secretion following a period of intensified diabetes management with its attendant increase in hypoglycemia. Similar hormonal defects with unawareness of symptoms can be induced in patients with diabetes (48, 49) and nondiabetics (50–52), some after a solitary episode of hypoglycemia. The current studies document the plasticity with which the CNS adjusts its acquisition of fuel to permit survival from natural and induced alterations in systemic glucose provision. Extrapolating our findings to patients with diabetes, the response that we describe is adaptive, given that it preserves glucose homeostasis and cognitive function in the face of recurrently limited fuel resources. However, from the standpoint of patient safety, symptoms and counterregulation may be triggered so late in the development of hypoglycemia that a seizure or loss of consciousness occurs prior to, or even after, adequate treatment has been completed. As such, this alteration may be viewed as maladaptive.

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