The Effects of Acute Hypoglycemia on Relative Cerebral Blood Flow Distribution in Patients With Type I (insulin-dependent) Diabetes and Impaired Hypoglycemia Awareness

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To examine the hypothesis that in diabetic patients with impaired hypoglycemia awareness the relative regional distribution of cerebral blood flow (rCBF) would be abnormal in a specific area, namely the frontal lobes, rCBF was examined in 20 type I diabetic patients, of whom 10 had a normal awareness of hypoglycemia and 10 had a history of impaired hypoglycemia awareness. rCBF was determined sequentially using single photon emission computed tomography (SPECT) during (1) normoglycemia (arterialized blood glucose 4.5 mmol · L^{-1}) and (2) hypoglycemia (blood glucose 2.5 mmol · L^{-1}) induced by a hyperinsulinemic glucose clamp technique. Distribution of the isotope, ^{99m}Tc-Exametazime, was detected using a single-slice multi-detector head scanner. A split-dose technique was used, with 250 MBq being injected during steady-state normoglycemia and 250 MBq during subsequent hypoglycemia. rCBF was estimated in 30 regions of interest, derived from a standard neuroanatomical atlas on two parallel slices at 40 and 60 mm above the orbitomeatal line (OML). No between-group differences in the pattern of overall rCBF or changes in regional tracer uptake were demonstrated. In comparison to the rCBF during normoglycemia, both patient groups exhibited significant changes in the pattern of rCBF during hypoglycemia, with increments of rCBF to both superior frontal cortices and the right thalamus and reduced rCBF to the right posterior cingulate cortex and the right putamen. This pattern of relative redistribution of rCBF during hypoglycemia was preserved in patients who had impaired hypoglycemia awareness.

THE DEPENDENCE of the brain on a continuous supply of glucose as its obligate fuel renders it vulnerable to neuroglycopenia. Some parts of the central nervous system are more vulnerable than others to neuroglycopenia: the middle layers of the cerebral cortex and the hippocampus are the most sensitive and the brainstem and spinal cord are the most resistant to hypoglycemic brain injury.[1] A rostrocaudal deterioration in function is also observed clinically, with the higher centers being affected at an earlier stage of neuroglycopenia.

In humans with type I (insulin-dependent) diabetes, the frontal lobes appear to be particularly vulnerable to the effects of acute hypoglycemia, as demonstrated by electroencephalogram and neuropsychological studies.[2,3] Studies of regional cerebral blood flow (rCBF) using single photon emission Computed tomography (SPECT) in nondiabetic and type I diabetic subjects have demonstrated a relative redistribution of rCBF in response to controlled hypoglycemia, with the greatest increments occurring in the frontal lobes.[4,5] This initially transient alteration in rCBF may become modified by repetitive exposure to neuroglycopenia. In a previous study in our laboratory, rCBF was measured using SPECT under normoglycemic conditions in type I diabetic subjects compared with nondiabetic subjects.[6] A relative increase in rCBF to both frontal lobes was observed in diabetic subjects, and the magnitude of this effect was greater in a subgroup who had a history of recurrent severe hypoglycemia. The increased rCBF in the frontal cortex of the diabetic patients in the basal state may therefore represent a chronic adaptive response to protect vulnerable areas of the brain against the potentially deleterious effects of recurrent and protracted neuroglycopenia. One aim of the present study was to replicate the increase in rCBF to the frontal lobes during hypoglycemia and, using a region-of-interest approach, to describe which of the frontal areas were particularly affected.

Impaired perception of the onset of hypoglycemia (hypoglycemia unawareness) is a common acquired clinical problem in many patients with type I diabetes, and is a major risk factor for developing severe hypoglycemia.[7-10] The etiology of this condition remains unclear. Repeated exposure to intermittent hypoglycemia diminishes the symptomatic and neuroendocrine responses to hypoglycemia and has been implicated as a potential cause of loss of hypoglycemia awareness.[11] The location of a putative glucose sensor within the human brain is unknown. Studies of the canine brain suggest that multiple sites throughout the central nervous system may be involved.[12] However, in the human brain, subjective conscious perception of hypoglycemia is likely to involve higher centers, including the cerebral cortex, and may be localized to specific regions such as the frontal lobes. Failure of recognition of hypoglycemia by the glucose sensor or failure of onward neural transmission from the receptor to the area of the brain that subserves hypoglycemic symptom perception and promotes activation of the integrated neuroendocrine response to hypoglycemia may underlie hypoglycemia unawareness. We therefore hypothesized that diabetic patients with impaired awareness of hypoglycemia may have an acquired localized

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cerebral abnormality within a specific region of the brain (the frontal lobes).

To examine this hypothesis, rCBF was studied in two matched groups of patients with type I diabetes, one with a history of chronically impaired awareness of hypoglycemia and the other with normal awareness. The groups were matched for historical frequency of severe hypoglycemia to ensure that unawareness of hypoglycemia was the sole variable under study.

SUBJECTS AND METHODS

Patients

Twenty patients with type I (insulin-dependent) diabetes were recruited to participate in the study. Ten patients had a history of impairment in the subjective ability to detect the onset of hypoglycemia (unawareness), and 10 had normal symptomatic warning of hypoglycemia (normal awareness). Impaired awareness of hypoglycemia was defined as a chronic impairment in the ability to perceive the onset of hypoglycemia of more than 2 years' duration, and was not related to the quality of glycemic control over this period. In addition to the clinical history, patients were selected by self-report of awareness of hypoglycemia on a seven-point visual analog scale ranging from normal (1) to absent (7) awareness. The nature of the symptoms patients used to identify the onset of hypoglycemia was determined by a questionnaire incorporating the common cardinal autonomic (neurogenic) symptoms of hypoglycemia (sweating, tremor, pounding heart, and hunger) and the neuroglycopenic symptoms (confusion, odd behavior, drowsiness, incoordination, and difficulty speaking).[13,14] Patients with normal awareness of hypoglycemia all scored 1 or 2 for awareness, stated that the nature and intensity of their hypoglycemic warning symptoms had remained unchanged since diagnosis, and reported that they perceived the onset of hypoglycemia predominantly by autonomic symptoms. The unaware patients all scored at least 4 on the awareness scale and described experiencing principally neuroglycopenic symptoms of hypoglycemia.

Results of routine home blood glucose monitoring by the patients with impaired awareness of hypoglycemia confirmed the frequent occurrence of asymptomatic biochemical hypoglycemia (capillary blood glucose <2.5 mmol $\cdot$ L^{-1}), which was not prevalent in the patients with normal awareness. The accuracy of this classification of the existing state of awareness of hypoglycemia through historical self-report had been confirmed by the inclusion of many of these patients in a larger prospective study to determine the frequency of severe hypoglycemia in patients with a history of impaired awareness of hypoglycemia.[10] This confirmed that the unaware patients were unable to detect the onset of hypoglycemia. A similar North American study has validated this approach,[15] demonstrating that diabetic patients who believe they have impaired awareness of hypoglycemia are invariably correct. A complete absence of hypoglycemic symptoms is extremely uncommon; however, in clinical practice many patients, particularly those with diabetes of long duration, describe a reduced ability to detect the onset of hypoglycemia, and this acquired defect is associated with an increased frequency of asymptomatic biochemical hypoglycemia and severe hypoglycemia.[10,15,16]

The two groups of patients were matched for age, sex, age at onset and duration of diabetes, insulin dose, and quality of glycemic control (Table 1). The two groups were from similar social classes (six of each group from social class 2 [managerial and technical] and four of each group from social class 3 [skilled manual]) and had a similar body mass index. The total glycosylated hemoglobin level was estimated; the nondiabetic range for our laboratory is 5% to 8%. One subject in each group was left-handed. Exclusion criteria for the study included a history of cerebrovascular, cardiovascular, or peripheral vascular disease, previous head injury, psychiatric illness, epilepsy (including hypoglycemia-induced convulsions), chronic alcoholism, hypertension, or any other systemic disease. Patients were excluded if they had other than minimal diabetic retinopathy as assessed by direct ophthalmoscopy, visual impairment, or clinical evidence of peripheral or autonomic neuropathy. All patients in both groups had experienced at least one episode of hypoglycemia in the preceding 2 years. However, the overall history of exposure to severe hypoglycemia based on retrospective reporting did not differ significantly between the two groups (Table 1). A similar history of exposure to severe hypoglycemia was an important precondition, since a significantly different experience of severe hypoglycemia between the two groups would have precluded the attribution of any observed differences in SPECT scanning to hypoglycemia unawareness per se. In addition, the quality of glycemic control in both groups was very similar.

Table 1. Sociodemographic Characteristics, Years of Education (total), NART Estimates of Premorbid Intelligence, AH4 Estimates of Current Intelligence, and Alderley Park State Anxiety Scores (APSAQ) for Aware and Unaware Diabetic Patients (mean ± SD)

Parameter	Aware	Unaware
Age	37.4 ± 5.1	35.5 ± 7.7
Sex (M/F)	7/3	7/3
Social class (2/3)	6/4	6/4
Age at onset (yr)	19.6 ± 9.5	22.1 ± 0.2
Duration of diabetes (yr)	17.9 ± 7.8	12.8 ± 4.4
Body mass index (kg/m^2)	24.2 ± 3.0	25.6 ± 2.7
Insulin dose (U/kg)	0.75 ± 0.2	0.72 ± 0.2
Hemoglobin A_1 (%)	10.3 ± 2.2	9.7 ± 1.0
Total episodes of previous severe hypoglycemia (n)		
0-5	8	6
>5	2	4
Intelligence		
Years of education	14.5 ± 2.4	13.7 ± 1.8
NART IQ (errors)	36.3 ± 6.5	35.4 ± 10.1
AH4 score	86.4 ± 15.3	78.3 ± 13.0
Anxiety		
APSAQ		
After first injection	6.2 ± 4.3	7.2 ± 6.2
After second injection	9.4 ± 9.2	7.3 ± 9.3

The intellectual abilities of both groups were similar, as estimated by years of education (total), scores on the National Adult Reading Test (NART), an estimate of premorbid intelligence and peak cognitive ability,[17] and scores on the Alice Heim 4 (AH4), an estimate of current intellectual function[18] (Table 1). Although these results do not represent an exhaustive battery of intelligence testing, they indicate that the two groups of patients were of comparable intellect and, in particular, that the unaware diabetic patients did not have significant intellectual damage.

Hypoglycemia Protocol

The patients were not studied if they had experienced symptomatic hypoglycemia or had recorded biochemical evidence of hypoglycemia (below 3 mmol $\cdot$ L^{-1}) in the 48 hours preceding the study. Blood glucose was carefully controlled throughout the study in all patients, using a modified manual hyperinsulinemic glucose clamp[19] adjusted to achieve three phased glycemic plateaus: (1) normoglycemia for 30 minutes (arterialized blood glucose, 4.5 mmol $\cdot$ L^{-1}),

(2) hypoglycemia for 30 minutes (blood glucose, 2.5 mmol · L^{-1}), and (3) restoration of normoglycemia (blood glucose, 4.5 mmol · L^{-1}). Overnight admission to the hospital before the study was not feasible, so the patients attended at midday, having received a reduced amount of their usual dose of short-acting (soluble) insulin before breakfast, and intermediate-acting (isophane) insulin was withheld. After breakfast, the patients fasted until midday. Starting at 12:00 noon, a continuous infusion of soluble insulin (human Actrapid; Novo Nordisk, Crawley, UK) was administered through an intravenous catheter in the antecubital fossa at a rate of 60 mU/m^2/min with a coincidental infusion of 20% dextrose at a variable rate to achieve the target blood glucose concentrations. The rate of glucose infusion was varied manually. Whole blood was sampled throughout the study at 5-minute intervals from a cannula placed retrogradely in a dorsal hand vein. The hand was maintained in a heated box at 60°C to achieve arterialized venous blood samples. Blood glucose was analyzed using an on-site Yellow Springs analyzer (2300 Stat; YSI, Yellow Springs, OH).

Physiological Measurements

Heart rate was recorded continuously using a three-lead electrocardiogram, and blood pressure was measured at 5-minute intervals by automated sphygmomanometry throughout the study. Respiratory end-tidal pCO_2 was measured at frequent intervals in the immediate preinjection and postinjection periods, using nasal cannulae. Formal scoring of symptoms was not performed during the study, because the physical restraints and time limits imposed by the scanning technique precluded regular assessment of symptoms. However, the aware patients all confirmed experiencing symptomatic hypoglycemia with normal perception of predominantly autonomic symptoms, whereas none of the unaware patients reported experiencing hypoglycemic symptoms other than modest neuroglycopenic symptoms that developed late in the study and were of no value in detecting the onset of experimental hypoglycemia.

Imaging Procedure

All patients were examined with a single-slice multi–detector dedicated head scanner (Multi-X 810; Strichman Medical Equipment, Boston, MA) after repeated injections of half-dose fractions of ^{99m}Tc-Exametazime (Amersham International, Amersham, UK). The single-photon (gamma) emitter, ^{99m}Tc-Exametazime (hexamethyl propylene amine oxime), is taken up avidly into brain cells on first pass after intravenous injection. Approximately 85% of the tracer is retained in situ, so the activity that is measurable for hours after the injection reflects the distribution of isotope in the immediate postinjection period. With 572-hole collimators, the maximum in-slice resolution of the scan is 7.5 mm (full width, half-maximum) by 15-mm slice thickness. The sensitivity of the instrument has been measured as 520 counts per second in a head-sized phantom containing 1 kBq/m.[20]

Each patient received an initial dose of 250 MBq injected as a bolus into an indwelling intravenous catheter, which had been inserted more than 1 hour previously. During the injection, the patient lay comfortably on the imaging table with eyes covered and ears unplugged. Ambient noise was kept to a minimum for 5 minutes after the start of injection. The patient's head was then positioned in a molded head rest with the help of two crossed light beams. To restrict movement, the head was fixed with pressure pads over the zygomatic arches. During the first scan, counts were obtained in two slices parallel to the orbital meatal line (OML), at 40 and 60 mm above the OML. After the first scan, hypoglycemia was induced as described earlier. The second dose of 250 MBq was then injected during resting conditions. During the second scan, the whole brain was scanned in parallel transaxial slices at 1-cm intervals from the OML upward.

Image Analysis

Local count densities were examined with a region-of-interest approach. Standard templates were derived from a neuroanatomical atlas[21] and fitted by aligning the outer border of the template with the 40% isocontour line of the brain activity map, that is, with the lower 40% of the intensity spectrum of the image removed. This method avoids arbitrary definition of regions of interest centered on local hot spots, which could introduce a bias. The reliability of this method has been demonstrated previously.[20] It is sufficient to allow detection of regional activation effects of approximately 5% in groups of 10 subjects.

Anxiety Assessment

To assess levels of anxiety, the Alderley Park State Anxiety Questionnaire (APSAQ)[22] was administered 5 minutes after each injection of radioisotope. State anxiety was low and did not differ within or between groups after each injection (Table 1).

Consent

The study protocol was approved by the local Medical Ethics Advisory Committee, and written informed consent was obtained from all patients.

Statistical Analysis

Regional tracer uptake was normalized by division through whole-slice uptake for each subject. The count densities of the second scan were corrected for activity remaining after the first injection. Current knowledge supports a frontal predilection for cerebral effects of hypoglycemia.[4,6,23,24] Therefore, multivariate analysis of variance (MANOVA) was performed for normalized regional isotope uptake at baseline and during hypoglycemia, including the anterior cerebral regions of interest (anterior cingulate and frontal cortex in both cerebral hemispheres and at both levels).

The MANOVA design had one between-subject variable with two levels (presence and absence of hypoglycemia awareness). There were four within-subject factors: region of interest with two levels (frontal and anterior cingulate), slice with two levels (upper and lower), glycemic status with two levels (normoglycemia and hypoglycemia), and cerebral hemisphere with two levels (right and left). The dependent variables were normalized isotope uptake in each of the eight anterior regions of interest for the two glycemic conditions, ie, right and left frontal and cingulate regions in the higher and lower transcerebral slices.

RESULTS

The actual blood glucose concentrations achieved during the study are shown in Fig 1. Target blood glucose concentrations were closely approximated and maintained in both patient groups throughout the study. No statistical differences in blood glucose concentrations between groups were apparent ($F = 0.07$, $P = .9$). Hemodynamic responses to hypoglycemia (heart rate and blood pressure) were also similar in both groups, and respiratory pCO_2 did not differ significantly between groups. Thus, for systolic blood pressure, results of the test of awareness/study interaction were not different ($F = 0.07$, $P = .8$). The corresponding values for diastolic blood pressure ($F = 0.85$, $P = .4$) and heart

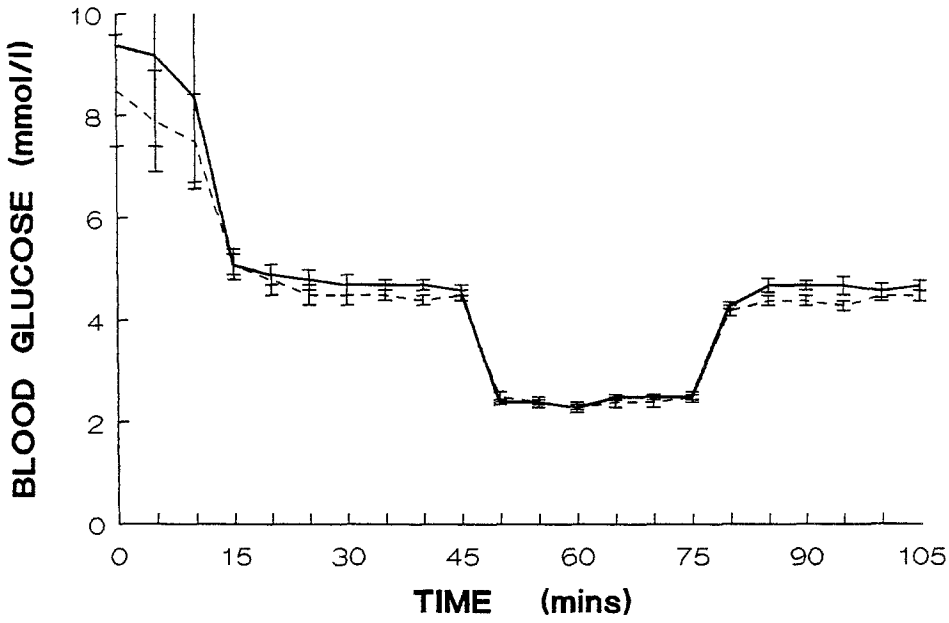

Fig 1. Blood glucose concentration plotted against time for aware (—) and unaware (– – – –) diabetic patients.

rate (F = 1.71, P = .21) also were not significantly different.

The MANOVA showed no overall effect of awareness on normalized isotope uptake in the combined regions of interest representing the anterior portion of the brain (the anterior cingulate and frontal cortex; F = 0.11, P = .74). There was a significant main effect of hypoglycemia in altering normalized regional isotope uptake across the anterior brain (F = 5.35, P = .03). Hypoglycemia therefore altered the regional uptake of technetium across all anterior regions (anterior cingulate and frontal cortex).

No interaction was observed between the state of awareness of hypoglycemia and the effect of hypoglycemia (F = 1.89, P = .19). Thus, the influence of hypoglycemia to alter the normalized regional isotope uptake in the anterior portions of the brain was independent of the state of awareness of hypoglycemia. There was a significant interaction between state of awareness of hypoglycemia and regional isotope uptake across the anterior regions (F = 7.46, P = .014), but post hoc MANOVA failed to attribute this effect specifically to either the anterior cingulate (F = 1.97, P = .177) or the frontal regions of interest (F = 1.49, P = .238). This suggests that the state of awareness of hypoglycemia does influence rCBF to the anterior brain in a distinctive but subtle way, and that this effect cannot be localized specifically to one of the delineated areas. This effect of awareness on rCBF is not influenced by hypoglycemia. No three-way interaction existed between state of awareness of hypoglycemia, acute experimentally induced hypoglycemia, and regional isotope uptake.

Since no differences were observed in terms of overall rCBF or changes in rCBF as shown by regional uptake of tracer between the two groups of diabetic patients (aware and unaware) in response to acute hypoglycemia, the results of both groups were pooled for the subsequent pairwise analysis to localize and examine the size of the effect of hypoglycemia in all 30 regions of interest in which measurements were made. In comparison to the isotope uptake in the basal (normoglycemic) state, a significant increase in isotope uptake was observed in the right thalamic cortex and in both frontal cortices during hypoglycemia. Table 2 summarizes whole-slice ratios at baseline and during hypoglycemia for all 30 regions of interest. The results in the right thalamic cortex must be regarded as exploratory, but the effect of hypoglycemia to increase relative isotope uptake and thus rCBF in the frontal cortex, which was significant in the planned MANOVA, can be accepted as a more robust finding.

DISCUSSION

This study has identified a relative redistribution of rCBF in response to controlled hypoglycemia in type I diabetic patients, that was independent of the state of awareness of hypoglycemia. In a previous study[6] in our laboratory under basal, ie, normoglycemic conditions, type I diabetic patients exhibited a similar relative increase in rCBF to both frontal lobes as compared with nondiabetic subjects; the magnitude of this effect was greater in a subgroup of diabetic patients who had a history of recurrent severe hypoglycemia. This suggested that the increased rCBF in the basal state, particularly to the frontal cortex in the diabetic patients, may be a chronic adaptive response to protect vulnerable areas of the brain against the effect of protracted neuroglycopenia.[6] The relative redistribution of rCBF during acute hypoglycemia observed in the present study, with relative frontal hyperemia, is consistent with this proposed protective adaptation.

The particular vulnerability of the frontal lobes to the metabolic insult of hypoglycemia has also been suggested previously by electroencephalogram and neuropsychological studies.[2,3] In the present study, the change in the rCBF pattern observed in response to acute hypoglycemia cannot be equated with an absolute increase in blood flow to the frontal lobes; the methodology used does not exclude the

Table 2. Count Densities in the Regions of Interest, Normalized to the Mean Count Density in All Regions of Interest for the Left and Right Hemispheres

Region	Left Hemisphere			Right Hemisphere		
	Baseline	Hypoglycemia	Difference (%)	Baseline	Hypoglycemia	Difference (%)
Lower slice						
Frontal	1.04 ± 0.04	1.04 ± 0.08	+0	1.05 ± 0.03	1.05 ± 0.07	−1
Anterior cingulate	1.10 ± 0.09	1.16 ± 0.21	+6	1.19 ± 0.07	1.20 ± 0.16	+1
Anterior temporal	1.09 ± 0.05	1.10 ± 0.10	+1	1.14 ± 0.05	1.08 ± 0.12	−6
Posterior temporal	1.08 ± 0.05	1.08 ± 0.11	+0	1.10 ± 0.05	1.06 ± 0.09	−4
Occipital	1.05 ± 0.06	1.08 ± 0.12	+2	1.05 ± 0.06	1.05 ± 0.07	+0
Calcarine	1.25 ± 0.08	1.21 ± 0.13	−4	1.27 ± 0.07	1.24 ± 0.16	−3
Posterior cingulate	0.94 ± 0.10	0.97 ± 0.16	+3	1.03 ± 0.09	0.95 ± 0.15	−8*
Caudate	0.96 ± 0.10	0.87 ± 0.17	−9	0.90 ± 0.12	0.92 ± 0.22	+2
Putamen	1.11 ± 0.07	1.11 ± 0.14	+1	1.06 ± 0.06	0.98 ± 0.13	−8*
Thalamus	1.07 ± 0.05	1.04 ± 0.14	−3	1.02 ± 0.06	1.11 ± 0.13	+9*
Upper slice						
Frontal	1.01 ± 0.03	1.05 ± 0.07	+4*	1.02 ± 0.04	1.07 ± 0.09	+6*
Anterior cingulate	1.18 ± 0.09	1.16 ± 0.17	+2	1.19 ± 0.06	1.24 ± 0.18	+5
Parietal	1.05 ± 0.04	1.05 ± 0.07	+0	1.05 ± 0.04	1.08 ± 0.08	+3
Occipital	1.05 ± 0.06	1.07 ± 0.09	+1	1.05 ± 0.06	1.05 ± 0.10	+0
Posterior cingulate	1.27 ± 0.08	1.24 ± 0.16	−3	1.26 ± 0.09	1.32 ± 0.17	+6

NOTE. Data were combined for both groups of diabetic patients.

possibility that a global reduction in CBF has occurred in response to hypoglycemia with a relatively smaller reduction of blood flow to the frontal lobes. This interpretation is unlikely in view of the results of other studies in which direct measurements of CBF were obtained.[4,5,23,24]

Although most studies of rCBF in nondiabetic and type I diabetic subjects have demonstrated an increase in total CBF in humans in response to acute hypoglycemia of approximately 20%, with a persistent increment in the early period following restoration of normoglycemia,[4,5,23,24] a recent study by Powers et al[25] reported no alteration in mean CBF in seven normal humans during progressive hypoglycemia to 2.8 mmol · L^{-1} . These differences may be explained by differences in the severity of the hypoglycemic stimulus, impaired rCBF responses in patients with diabetes, and important clinical differences within the diabetic patient groups studied. Tallroth et al,[4,5] using a more severe hypoglycemic stimulus (venous blood glucose, 2.0 mmol · L^{-1}), produced an increase in total CBF of approximately 20% both in nondiabetic and in diabetic subjects. In the nondiabetic subjects, a significant alteration was observed in the relative distribution of CBF, with the highest increments in CBF found in the frontal and parietal lobes. In the diabetic patients, the magnitude of the response to hypoglycemia was smaller, inversely related to the initial blood glucose concentration, and more uniform.[5] This latter difference with the present study may reflect the longer duration of diabetes of their subjects, many of whom had developed diabetes in childhood. The developing brain is particularly susceptible to the adverse effects of hypoglycemic brain injury,[26-28] and may have a reduced capacity to enhance blood flow in a regionally selective manner in response to subsequent hypoglycemia. In addition, diabetic patients have been shown to exhibit impaired cerebral autoregulation and abnormal cerebrovascular reactivity.[29,30] Whether the observed changes in rCBF are dependent on the extent of the hypoglycemic stimulus and influenced by the duration of diabetes and presence of microangiopathic complications of the disease requires further study.

During normoglycemia, the unidirectional blood-to-brain flux of glucose operates in considerable excess of the cerebral glucose utilization (phosphorylation) rate.[31-33] However, under increasing hypoglycemic conditions, blood-brain glucose transport will decline and emerge as the rate-limiting factor.[34-37] The rapid increase in CBF observed in response to acute hypoglycemia may attenuate the degree of neuroglycopenia by increasing the availability of glucose. A modest local increase in glucose supply may occur through localized hyperemia secondary to recruitment of capillaries, thereby increasing the capillary bed area and thus potentially increasing glucose transport.[32]

One aim of the present study was to explore the pathogenesis of chronic hypoglycemia unawareness by comparing rCBF under normoglycemic and hypoglycemic conditions in two groups of patients discordant for awareness of hypoglycemia but otherwise closely matched. No overall effect of awareness on the distribution of rCBF was observed under basal or hypoglycemic conditions. Furthermore, the relative redistribution of rCBF in response to acute hypoglycemia was identical both in diabetic patients who had normal awareness of hypoglycemia and in those with unawareness. However, a significant interaction between awareness of hypoglycemia and regional isotope uptake was observed across the anterior brain, which was not affected by hypoglycemia. Although the pathogenesis of chronic hypoglycemia unawareness has not been elucidated, the present study implies that differential rCBF to the anterior brain may be implicated. The possibility cannot be discounted that although the relative redistribution of rCBF in response to hypoglycemia appeared to be identical, the absolute magnitude of the response was different in the unaware diabetic patients. Previous exposure to recurrent

severe hypoglycemia may be a more potent causal factor in determining the abnormal pattern of rCBF than the existing state of awareness of hypoglycemia. Although our two groups were matched for frequency of severe hypoglycemia, the intensity, duration, and biochemical severity of the episodes might have been greater in the unaware group. The possibility that chronic hypoglycemia unawareness is caused by a diminished or delayed central activation of the autonomic nervous system, secondary to an altered glycemic threshold for activation of the autonomic nervous system, has been suggested previously.[16,38-43]

The present methodology is not sufficiently sensitive to detect a functional abnormality confined to a small and highly specific area of the brain (such as the hypothalamus) that may contain a putative glucose sensor. However, in animals, the response to hypoglycemia appears to involve widespread areas of the brain,[12] and the present study of rCBF in diabetic humans suggests the coexistence of a diffuse functional abnormality in the anterior brain, which may be implicated in the impaired perception of hypoglycemia. The prefrontal areas of the cortex are closely connected to subcortical areas, and localized dysfunction could theoretically reduce the ability of the brain to perceive symptomatic hypoglycemia. In addition, these studies of rCBF suggest that specific areas of the brain have differential sensitivities to neuroglycopenia, and that adaptive mechanisms may develop for their protection.

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