Importance of Cerebral Blood Flow to the Recognition of and Physiological Responses to Hypoglycemia

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During hypoglycemia, cerebral blood flow (CBF) does not increase significantly until peripheral glucose levels are very low (2.0 mmol/l), that is, well below the blood glucose threshold for impairment of cognitive function (3.0 mmol/l). Because increased rates of cerebral blood flow will increase glucose transport, a failure of flow to rise earlier, before brain function is threatened, might be considered maladaptive. To examine the influence of inducing an earlier rise in CBF during hypoglycemia, eight healthy volunteers participated in three studies using a randomized, placebo-controlled design. In all three studies, a hyperinsulinemic (60 mU · m^2 · min^{-1}) clamp was used to maintain blood glucose levels at 4.5 mmol/l for 60 min. Thereafter, for EUGACZ, blood glucose was maintained at 4.5 mmol/l from 60 to 170 min and at 90 min from the start of this study, and 1-g acetazolamide i.v. was given to induce an early rise in CBF; for HYPO-ACZ, glucose was lowered over 20 min to 2.8 mmol/l and kept at that level for 90 min, and acetazolamide was given 90 min from the start of this study; and for HYPO-CON, glucose was treated as in HYPO-ACZ, and matching placebo was given in place of acetazolamide. Injection of acetazolamide was associated with a 30% rise in right (95% CI 24–34%) and left (20–32%) middle cerebral artery velocity (an index of CBF) during euglycemia without any change in hypoglycemia awareness or counterregulatory hormone levels. When glucose was lowered to 2.8 mmol/l, acetazolamide caused a similar rise in middle cerebral artery velocity in the HYPO-ACZ study. However, all subjects were less "aware" of hypoglycemia, had fewer adrenergic symptoms (sweating, palpitations, tremors; all $P < 0.05$), and had lower plasma epinephrine levels (1,026 vs. 1,790 pmol/l; −764 [437 to 1,097] pmol/l, point estimate of difference [95% CI]; $P < 0.001$), compared with the HYPO-CON study, whereas levels of other counterregulatory hormones and norepinephrine were similar. Cognitive function (latency of the P300 evoked response) was unaffected by increasing CBF. In conclusion, enhanced rates of cerebral blood flow at the onset of systemic hypoglycemia are associated with diminished perception of low blood glucose levels and attenuation of the epinephrine counterregulatory response. These findings suggest that augmenting cerebral blood flow leads to an enhanced rate of substrate delivery to the central nervous system. *Diabetes* 829–833, 1997

Under normal circumstances, glucose is the only fuel that neuronal tissue uses as an energy source. Because the brain can neither synthesize nor store more than a few minutes' worth of glucose, a continuous supply from the systemic circulation is essential for normal brain function. Thus, it might be expected that during hypoglycemia, there would be an early increase in cerebral blood flow (CBF) to increase substrate delivery as peripheral glucose levels fall below normal. In fact, a detectable rise in CBF only occurs after blood glucose has fallen well below the glycemic threshold for cognitive impairment (1,2). Teleologically, the failure of CBF to increase at an earlier stage (i.e., before the onset of cognitive impairment) appears to be maladaptive.

Recently, we have reported that a caffeine-induced reduction in CBF caused both intensity of warning symptoms and hormonal counterregulatory responses to be markedly enhanced during mild (3.8 mmol/l) and moderate (2.8 mmol/l) hypoglycemia in healthy volunteers and diabetic patients (3,4).

The aim of this study was to investigate whether increasing CBF, and consequently increasing substrate supply to the brain, will blunt the sympathoadrenal responses to hypoglycemia. For this purpose, we induced a rise in CBF while reducing blood glucose to levels above the usual glycemic threshold for a hypoglycemia-mediated rise in CBF. Acetazolamide, a carbonic anhydrase inhibitor, was used to increase CBF. Previous studies have shown that intravenous injection of acetazolamide produces an immediate rise in brain blood flow that reaches a maximum (increasing flow by as much as 75%) after 30 min and declines, thereafter, with a half-life of 120 min (5,6).

RESEARCH DESIGN AND METHODS

Eight healthy volunteers (four men aged 22–40 years) gave written, informed consent for the study, which was approved by the local hospital ethics committee. Each subject participated in three studies with at least 1 week between each study.

All studies were performed in The Metabolism Research Unit at the Royal Bournemouth Hospital. On the morning of the study, subjects were admitted fasting. Two intravenous catheters were inserted; one was inserted in an antecubital

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CBF, cerebral blood flow; VAS, visual analog scales; V_{MCA}, middle cerebral artery velocity.

vein for infusion of insulin and 20% glucose solution, and a second was inserted retrograde into a dorsal hand vein for sampling of arterialized venous blood. The hand was placed in a heated box (60°C) and the cannula kept patent by a 154-mmol/l NaCl infusion. Potential distractions such as conversation and other background noise were minimized throughout each study. After insertion of the cannulae, baseline measurements were made of middle cerebral artery velocity (V_{MCA}) using a transcranial Doppler technique (SciMed, Bristol, U.K.) as previously described (7). Although measurement of V_{MCA} assumes that caliber changes in the vessel are small (8), previous studies have indicated that alterations in V_{MCA} reflect similar changes in global and hemispheric CBF during euglycemia and hypoglycemia (3,9).

Cognitive function and awareness of hypoglycemia. Cognitive function was examined using P300 auditory evoked responses (Medelec, Surrey, U.K.) (10). The P300 component of event-related potentials appears to be a reliable indicator of cognitive function and relates incoming sensory information to memory-updating processes. Scalp electrodes were placed on the vertex and right and left mastoids. P300 latency, the interval from the stimulus to the peak of the evoked potential, was obtained during a task in which the subjects silently count high-pitched clicks delivered in a train of frequent low-pitched and infrequent high-pitched clicks.

Subjects then completed visual analog scales (VAS) to assess symptoms characteristically associated with hypoglycemia (irritability, palpitations, tingling, trembling, sweating, hunger, feeling faint, dizziness, anxiety, difficulty thinking, and blurred vision). They were asked to score the symptoms on a 100-mm straight line with the extremes of the line marked for each symptom as "absent" and "severe." The lines were marked at a point appropriate to the intensity of each symptom. Symptoms were compared using cumulative scores and thereafter by dividing them into "autonomic" (trembling, hunger, palpitations, anxiety, tingling, sweating) and "neuroglycopenic" (irritability, feeling faint, dizziness, blurred vision, difficulty thinking) groups. The subjects were told that their blood glucose might be lowered at some stage during each of the visits, but they were not told the level at any time. At recruitment, all subjects were informed of the likely symptoms associated with low blood glucose levels. After injection of acetazolamide, symptoms of headache and flushing are usually mild and transient and frequently not reported by subjects.

Hormone levels. Blood was taken from the vein draining the heated hand for subsequent measurement of epinephrine, norepinephrine, growth hormone, and insulin concentration. Plasma insulin and growth hormone levels were measured by double antibody radioimmunoassays and catecholamines by a radioenzymatic technique (Amersham, Arlington Heights, IL).

After the baseline measurements, a euglycemic-hypoglycemic, hyperinsulinemic (60 mU · m^2 · min^{-1}) glucose clamp (11) was used to maintain blood glucose levels at 4.5 mmol/l for 60 min (t = 0–60). Thereafter, for EUG-ACZ, blood glucose was maintained at 4.5 mmol/l for an additional 110 min (t = 60–170) and 1-g i.v. acetazolamide was given at 90 min to induce an early rise in CBF; for HYPO-ACZ, blood glucose was lowered over 20 min to 2.8 mmol/l and kept at that level for 90 min (t = 80–170), and acetazolamide was given 90 min from the start of this study; and for HYPO-CON, glucose was treated as in HYPO-ACZ, and matching placebo was given in place of acetazolamide.

The order of the studies was randomized, and HYPO-ACZ and HYPO-CON studies performed using a double-blind design. All the above measurements were repeated every 10–30 min.

Statistical analyses. Overall differences between serial measurements were examined by the use of summary measures (12). Summary responses for each individual were calculated as area under the curve (AUC) using the trapezoid method; if significantly different, contrasts in group means were subsequently compared by paired Student's t tests. Where data were not normally distributed, comparisons were made after logarithmic transformation or Wilcoxon's signed-rank tests. Results are expressed as individual means with point estimates of differences between means or medians and 95% CIs. Otherwise data are shown as means ± SE or medians ± interquartile range.

TABLE 1
Mean ± SE blood glucose, plasma insulin, pCO_2, hematocrit, heart rate, mean arterial pressure, and cognitive function (latency of P300 evoked response) at baseline and averaged over the final 20 min of each study

Variable	Baseline	Glucose 2.8/4.5 mmol/l
Glucose (mmol/l)		
EUG-ACZ	4.42 ± 0.12	4.53 ± 0.04
HYPO-CON	4.68 ± 0.15	2.77 ± 0.03
HYPO-ACZ	4.43 ± 0.07	2.78 ± 0.04
Insulin (pmol/l)		
EUG-ACZ	55 ± 5	630 ± 30
HYPO-CON	60 ± 5	590 ± 12
HYPO-ACZ	56 ± 4	595 ± 21
pCO_2 (kPa)		
EUG-ACZ	4.9 ± 0.1	4.9 ± 0.1
HYPO-CON	4.9 ± 0.1	4.9 ± 0.1
HYPO-ACZ	5.0 ± 0.1	4.9 ± 0.2
Hematocrit (%)		
EUG-ACZ	36.4 ± 1.2	35.8 ± 1.2
HYPO-CON	37.9 ± 2.1	37.2 ± 2.1
HYPO-ACZ	35.7 ± 2.0	34.8 ± 1.9
Heart rate (beats/min)		
EUG-ACZ	69 ± 3	71 ± 3
HYPO-CON	67 ± 4	76 ± 4*
HYPO-ACZ	67 ± 3	73 ± 2*
Mean arterial pressure (mmHg)		
EUG-ACZ	80 ± 3	79 ± 3
HYPO-CON	80 ± 2	74 ± 3*
HYPO-ACZ	80 ± 3	75 ± 3*
Latency of P300 evoked response (ms)		
EUG-ACZ	297 ± 6	298 ± 5
HYPO-CON	298 ± 5	319 ± 5*
HYPO-ACZ	302 ± 5	317 ± 3*

Data are means ± SE. $P < 0.05$ vs. EUG-ACZ study.

RESULTS

In all three studies, average blood glucose and plasma insulin levels were similar at baseline, after 60 min of euglycemia, and during hypoglycemia (Table 1). Coefficients of variation for blood glucose levels achieved during each stage were <5%. Arterialized pCO_2 and hematocrit did not change significantly throughout each study (Table 1).

Hemodynamics. V_{MCA}, heart rate, and blood pressure were similar at baseline in all three studies and after 60 min of euglycemia (Fig. 1, Table 1). After injection of acetazolamide, right and left V_{MCA} increased by 20 cm/s (95% CI 16–23) and 22 cm/s (95% CI 14–28), respectively (both $P < 0.0001$), in the EUG-ACZ and increased by 18 cm/s (95% CI 14–22) and 19 cm/s (95% CI 13–24) (both $P < 0.0001$) in the HYPO-ACZ studies. There was no change in V_{MCA} throughout the HYPO-CON study. When blood glucose was lowered to 2.8 mmol/l, heart rate increased in both hypoglycemia studies ($P < 0.05$) and mean arterial pressure fell ($P < 0.05$); however, both were unaffected by acetazolamide and were unchanged during euglycemia (Table 1).

Counterregulatory hormone levels. Baseline values for counterregulatory hormone levels were similar at the start and did not significantly change during the euglycemic phase of each study or throughout the EUG-ACZ study (Fig. 2, Table 2). During both hypoglycemia studies, areas under the concentration/time curves for epinephrine, norepinephrine glucagon, and growth hormone were higher, compared with the EUG-ACZ study (all $P < 0.02$) (Table 2). The AUC for epinephrine was significantly less in the HYPO-ACZ, compared with HYPO-CON study ($P < 0.02$). When blood glucose was maintained at 2.8 mmol/l, achieved plasma epinephrine levels were markedly attenuated after acetazolamide ($P <$

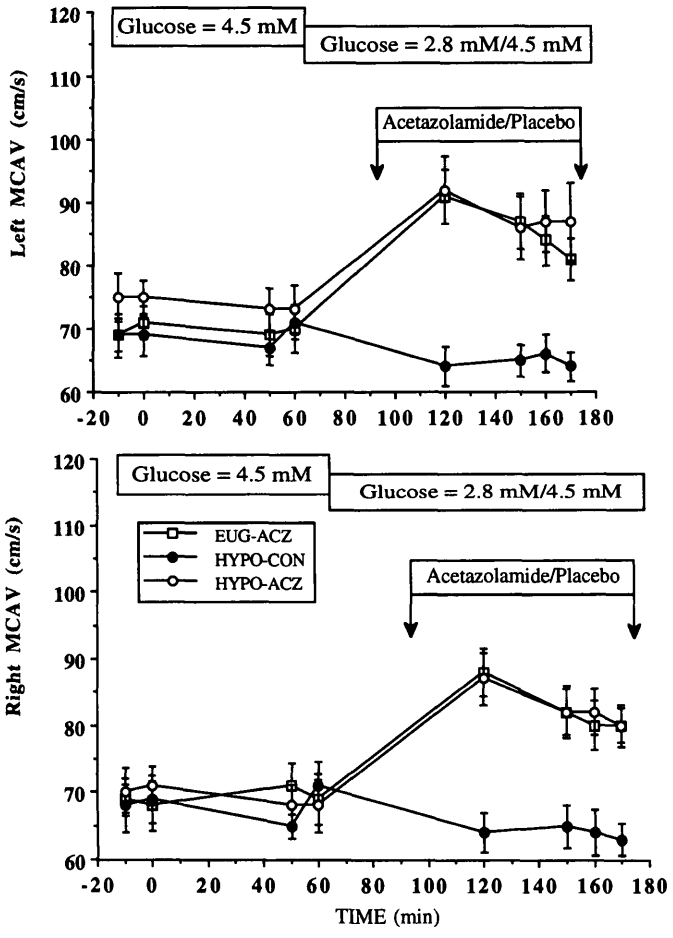

FIG. 1. Right and left V_{MCA} (an index of CBF). Data are shown as means ± SE.

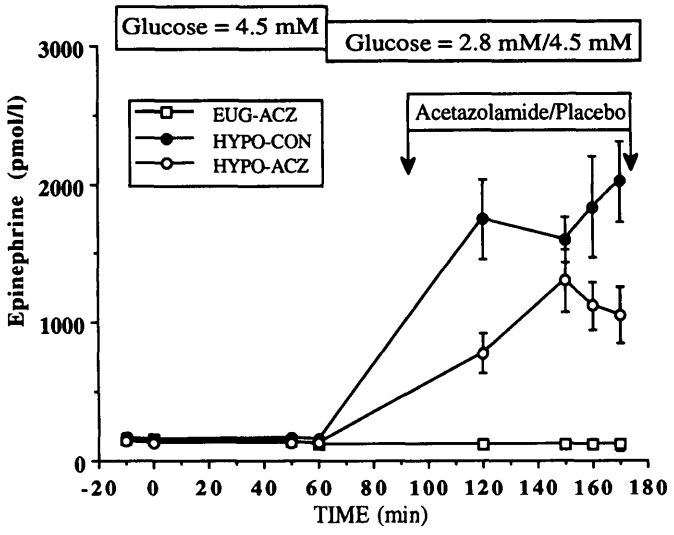

FIG. 2. Plasma epinephrine levels. Data are shown as means ± SE. Area under curve for epinephrine was significantly less in the HYPO-ACZ study, compared with HYPO-CON study ($P < 0.02$).

0.001), whereas levels of the other counterregulatory hormones were similar.

Symptoms and cognitive function. Baseline symptom scores and cognitive function (latency of the P300 evoked potential) were similar at the start of each study (Figs. 3 and 4). When blood glucose was lowered to 2.8 mmol/l, all subjects reported less "awareness" after acetazolamide (HYPO-ACZ) associated with diminished intensity of warning symptoms (median cumulative symptom scores 116 vs. 227 mm; 111 mm [95% CI 55–232]; $P < 0.02$), compared with the HYPO-CON study (Fig. 3). The intensity of autonomic (tremors, sweating, palpitations) but not neuroglycopenic symptoms was affected by acetazolamide at this glucose level (Fig. 4). Awareness in the EUG-ACZ study was unaffected by acetazolamide. Despite less intense symptoms, the deterioration in cognitive function (latency of the P300 evoked response) was similar in both hypoglycemia studies (19.5 vs. 15.3 ms; 4.2 ms [95% CI –5 to 20], NS) (Table 1).

DISCUSSION

Because the brain is normally dependent on a continuous supply of glucose from the peripheral circulation to maintain normal function, it might be expected that during hypoglycemia, CBF would increase before the blood glucose threshold for cognitive impairment is reached. In fact, brain blood flow does not increase until blood glucose levels have fallen to very low levels (<2.0 mmol/l), well below the threshold for cognitive impairment (3.0 mmol/l) (1,2,13). Here, while maintaining blood glucose above the threshold, which normally stimulates a rise in CBF during hypoglycemia, V_{MCA} (an index of CBF) increased by almost 30% after injection of acetazolamide associated with less "awareness," less intense "adrenergic" warning symptoms, and an attenuated epinephrine response to hypoglycemia. In contrast to the effect of increased CBF on hypoglycemia awareness, the impairment in cognitive function caused by mild hypoglycemia was unaffected by acetazolamide.

Glucose delivery to neural tissue involves substrate delivery via the cerebral circulation and transport across the blood-brain barrier by means of the specific glucose transport protein, GLUT1 (14). Thus, glucose extraction from the cerebral circulation is directly related to the available surface area, as well as blood flow and the quantity and activity of GLUT1 transporters. The consequences of changing blood flow on brain glucose extraction is dependent on the nature of the

TABLE 2
Counterregulatory hormone levels during euglycemia and hypoglycemia

Variable	Protocol	AUC
Epinephrine (pmol · ml^{-1} · min^{-1})	EUG-ACZ	23 ± 3
	HYPO-CON	155 ± 19*
	HYPO-ACZ	91 ± 15*‡
Norepinephrine (nmol · l^{-1} · min^{-1})	EUG-ACZ	233 ± 22
	HYPO-CON	283 ± 23*
	HYPO-ACZ	262 ± 26*
Glucagon (ng · l^{-1} · min^{-1})	EUG-ACZ	7064 ± 384
	HYPO-CON	9439 ± 682*
	HYPO-ACZ	8988 ± 552*
Growth hormone (μg · l^{-1} · min^{-1})	EUG-ACZ	793 ± 153
	HYPO-CON	1238 ± 119*
	HYPO-ACZ	1637 ± 262*

Data are areas under the concentration/time curve. *$P < 0.02$ vs. EUG-ACZ protocol; ‡$P < 0.02$ vs. HYPO-CON protocol.

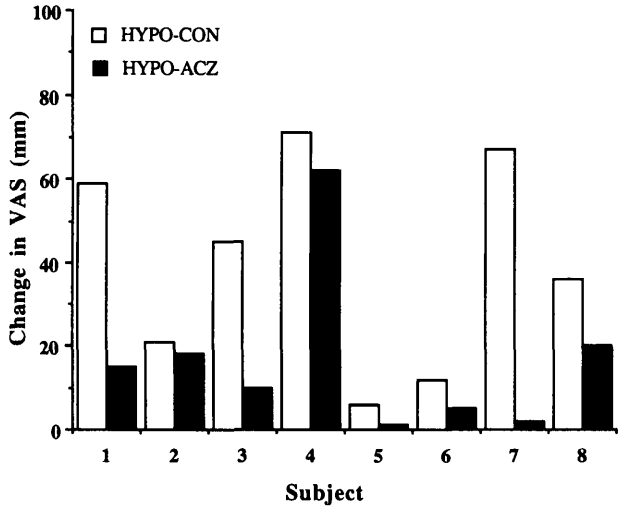

FIG. 3. Individual subject values for "awareness of hypoglycemia." Results are shown as change from baseline in VAS assessment when blood glucose was maintained at 2.8 mmol/l. The VAS consisted of a 100-mm straight line with the extremes (0 and 100 mm) marked as "not hypoglycemic" and "severely hypoglycemic." Subjects mark the scale at a point appropriate to the intensity of their symptoms.

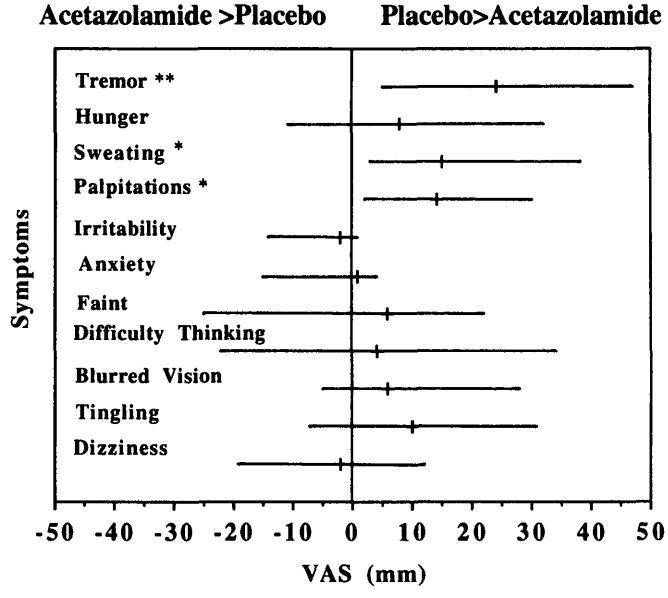

FIG. 4. Differences (median ± 95% CI) in individual symptom scores (placebo minus acetazolamide) using changes from baseline on VAS during hypoglycemic phase (2.8 mmol/l) of paired acetazolamide and placebo-control studies. *P < 0.05 and **P< 0.02 symptoms for which confidence limits were entirely positive.

increased flow, that is, increasing linear flow to be above-normal causes only a small increase in glucose transport as the blood-brain barrier's permeability to glucose is diffusion limited (15). However, if flow increases as a consequence of capillary recruitment, this will substantially increase the area available for glucose transport. Increasing the number and/or activity of glucose transporters will also enhance brain glucose extraction; however, this effect is probably important only after chronic sustained hypoglycemia rather than during acute lowering of blood glucose levels (16).

The higher centers responsible for control of the hormonal and sympathoadrenal responses to hypoglycemia appear to be located within the ventromedial hypothalamus (17). In this study, increasing brain blood flow attenuated the epinephrine response to moderate hypoglycemia, whereas levels of other counterregulatory hormones were unaffected, suggesting that brain areas involved in triggering release of counterregulatory hormones may be differentially sensitive to fluctuations in substrate supply via the circulation. Although there are widespread regional differences in resting and hypoglycemia-stimulated increases in brain blood flow (18), it is not known whether there are similar regional variations in the responses of cerebral glucose transport mechanisms to low blood glucose levels.

In relating changes in V_{MCA} to alterations in CBF, measurement of velocity assumes that caliber changes in the vessel are small, although under certain circumstances (e.g., exercise), this assumption may be erroneous (8). However, studies at rest directly comparing blood flow with velocity have shown that transcranial Doppler is a valid method for assessing cerebral vasoreactivity and that changes in CBF may be reliably evaluated by measurement of V_{MCA} during euglycemia and hypoglycemia (3,9). After injection of acetazolamide, Dahl et al. reported highly significant correlations between transcranial Doppler and regional CBF changes (measured by xenon inhalation and SPECT scanning) in normal subjects and in patients with cerebrovascular disease (19–21). The rise in CBF after administration of acetazolamide has been attributed to vasodilation of small arterioles in response to a reduction in brain tissue pH (22). In animals, the acetazolamide-induced rise in CBF appears to be a consequence of an increase in the number of capillaries perfused in a variety of brain regions (23).

During hypoglycemia, the rise in CBF involves both β-adrenergic and non–β-adrenergic mechanisms without any change in cerebral autoregulation (24). It is possible that acetazolamide-induced systemic vasodilation may have influenced the subsequent hormonal counterregulatory responses. However, the lack of significant changes in hormone and norepinephrine levels during the euglycemic control study makes this unlikely. As blood glucose levels fall below normal, changes in CBF and V_{MCA} do not correlate with alterations in systemic blood pressure or cardiac output (9). A similar lack of correlation between peripheral hemodynamic changes and CBF has been reported in patients with severe head injuries in whom cerebral autoregulation is impaired (25). Furthermore, during hypoglycemia, there does not appear to be a dose-response relationship between plasma catecholamine levels and CBF, as assessed by positron emission tomography (26).

In healthy volunteers subjected to prolonged hypoglycemia and patients with IDDM whose treatment results in nearly normal glycosylated hemoglobin levels, cerebral metabolism can be maintained as a consequence of accelerated brain glucose uptake. However, this adaptation of brain glucose metabolism to prolonged or recurrent hypoglycemia is associated with blunting of the hormonal counterregulatory responses and hypoglycemia unawareness (27,28). The present study suggests that enhancing substrate delivery by the cerebral circulation can also attenuate the hormonal responses to and perception of hypoglycemia without altering the normal cognitive responses to acute blood glucose lowering. This might be considered disadvantageous. If an

individual is dependent on the adaptive capability of brain glucose metabolism rather than symptomatic awareness for protection against low blood glucose levels, blood glucose levels would not have to fall much farther before the patient would be too neuroglycopenic to take appropriate action (27,28). The use of both male and female subjects may also be relevant because the effects of hypoglycemia on cognitive function appear to be influenced by sex, with women demonstrating less impairment of neuropsychological function than men during hypoglycemia (29).

In conclusion, enhanced rates of cerebral blood flow at the onset of moderate systemic hypoglycemia are associated with diminished perception of low blood glucose levels and attenuation of the epinephrine counterregulatory response. These findings suggest that enhancing cerebral blood flow leads to an enhanced rate of substrate delivery to the central nervous system.

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