Hypoglycemic Thresholds for Cognitive Dysfunction in Humans

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Nineteen healthy adult volunteers were studied to define the nature of and threshold for the cognitive dysfunction that occurs during insulin-induced hypoglycemia. The P300 cerebral event-related potential is an electrophysiological correlate of cognitive decision-making processes that can be measured in response to either an auditory or visual stimulus. P300 and reaction time (RT) were recorded from a visual stimulus under euglycemic conditions and at plasma glucose concentrations of 3.3 and 2.6 mM during insulin infusion in 10 subjects. Reducing plasma glucose levels to 3.3 mM was not associated with an increase in either the latency or amplitude of the P300 component or a change in RT. However, further lowering of plasma glucose to 2.6 mM resulted in an increase in the latency of P300 and a prolongation in RT. Similar changes were seen for the auditory P300 in experiments performed on 9 additional subjects in which both auditory and visual stimuli were presented. The prolongation of P300 did not correct immediately when plasma glucose was raised to basal levels with intravenous glucose but returned to normal 45–75 min later, after ingestion of a carbohydrate-containing meal. Analysis of another event-related potential, P140 (a measure of the sensory processes), showed no change in response to hypoglycemia. Prolongation of RT paralleled the prolongation of P300 latency, suggesting that motor processes were not altered. Therefore, hypoglycemia appears to induce abnormalities in decision-making processes. This study shows that *1*) insulin-induced hypoglycemia results in cognitive dysfunction when plasma glucose is between 3.3 and 2.6 mM on average, 2) decision-making processes rather than sensory or motor processes appear to be predominantly affected, 3) both auditory or visual P300 and RT were affected, 4) recovery of the cortical dysfunction may lag behind the return of plasma glucose to normal by 45–75 min, and 5) individual sensitivity to the adverse effects of hypoglycemia on cortical function appears to exist, but the physiological basis of this finding is not known.
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Considerable data are available that indicate that normalization of plasma glucose concentrations in patients with type I (insulin-dependent) diabetes can reduce the risk of complications (1). Therefore, more aggressive insulin regimens are being used to achieve tighter control of blood glucose. However, data from the Diabetes Control and Complications Trial study group (2) demonstrated that aggressive regimens of insulin replacement are associated with a threefold greater risk for hypoglycemia than conventional insulin therapy. The concern that these aggressive regimens may result in long-term adverse effects on cognitive function has not been systematically addressed, in part because the optimal method of detecting early cognitive dysfunction during mild hypoglycemia has not been determined.

Event-related brain potentials, which reflect the timing of sensory and cognitive processes, can be recorded during certain cognitive tasks. One easily recorded component is P300, a brain potential related to decision time (3–5). Its latency reflects the sensory and cognitive processing time associated with decision making, independent of response organization and execution. This study examined changes in P300 latency compared with another measure of cerebral function, reaction time (RT), to define the hypoglycemic thresholds for changes in cognitive event-related potentials and to define the brain functions most affected by insulin-induced hypoglycemia.

RESEARCH DESIGN AND METHODS

Studies were performed on 19 healthy right-handed volunteers (9 men, 10 women). The mean ± SE age, weight, and

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body mass index were 26.8 ± 1.3 yr, 67.6 ± 2.8 kg, and 22.8 ± 0.7 kg/m^2, respectively. All were within 20% of ideal body weight, and none had a personal or family history of diabetes. Women were studied in the preovulatory phase of the menstrual cycle. The studies were performed in the Clinical Research Center of the University of Chicago after written informed consent was obtained. The experimental protocol was approved by the institutional review board.

All studies were performed beginning at 0800 after a 10- to 12-h overnight fast. Subjects were on a weight-maintenance diet before the study. During each experiment, an intravenous sampling catheter was inserted in a retrograde direction in a dorsal vein of the left hand with its tip in place as distally as possible. The hand was kept in a heating blanket to ensure arterialization of the venous sample. An infusion catheter was inserted into the antecubital vein of the right arm.

After a 30-min baseline period, a constant infusion of insulin (14.4 nM · kg^{-1} · min^{-1}) was administered. Glucose was infused at a variable rate to maintain plasma glucose at baseline levels. After this period, the glucose infusion was decreased to allow blood glucose to fall to 3.3 mM for 75 min and then to 2.6 mM for an additional 75 min. The insulin infusion was then discontinued, and glucose was infused to raise the plasma glucose to baseline over 45 min. Subjects then consumed a high-carbohydrate meal within 30 min. The experiment was thus divided into six periods according to plasma glucose: baseline, euglycemic clamp, 3.3-mM clamp, 2.6-mM clamp, return to baseline, and postmeal. Experimental measurements were made three times during the final 30 min of each period.

To control for practice effects and the effects of fatigue on tests of cerebral function, each subject underwent an additional study on a separate occasion. The two studies were identical in all respects except that, during the control study, the variable glucose infusion was adjusted to clamp the plasma glucose at the basal euglycemic level throughout. The order of the studies was randomized. Subjects were not told in advance which study would be performed.

Glucose, insulin, and counterregulatory hormones. During each of the experimental periods, epinephrine, glucagon, cortisol, and growth hormone measurements were obtained at 10-min intervals. Glucose concentrations were measured every 5 min throughout each study with a YSI analyzer (model 23A; Yellow Springs, OH). Plasma glucagon (6) and serum free insulin (7) were measured by radioimmunoassay. Plasma catecholamines were extracted and then separated by high-performance liquid chromatography (8). Growth hormone was measured by radioimmunoassay (9) and cortisol by competitive binding assay (10). Potassium was measured with a Beckman Astra system reagent kit (Brea, CA) at baseline and every 2 h during the study. A variable infusion of potassium was administered as needed to maintain potassium concentrations >3 mM.

Signs and symptoms of hypoglycemia. At 10-min intervals throughout each study, the presence or absence of signs and symptoms of hypoglycemia was determined according to a modification of techniques proposed by Hoeldtke et al. (11). The signs of hypoglycemia that were evaluated included changes in blood pressure and pulse rate and objective evidence of sweating and neuroglycopenia, i.e., drowsiness, slurred speech, and confusion. The symptoms of hypoglycemia recorded were palpitations, diaphoresis, anxiety, blurred vision, and difficulty thinking or concentrating. Symptoms were rated as present or absent.

Simple RT to visual stimulus. During each of the six experimental periods described above, subjects were required to perform behavioral tasks as tests of cerebral and cognitive performance. The RT task required subjects to press a hand-held button immediately on observing the illumination of a red 4-mm-diam light-emitting diode (LED) centered on a 38 × 46-cm black screen. The RT task was administered as a series of blocks, each consisting of 24 trials. On 16 of these trials, a green warning LED located 4° to the left or right of the red LED preceded the illumination of the red LED by 1.5 or 2.5 s. The intertrial interval was 4, 6, or 8 s. The RT (i.e., interval between illumination of the central red LED and depression of the hand-held button) was recorded in milliseconds for each trial by an Apple IIe microcomputer, which controlled the stimuli and digitized event-related potentials. Trials with RTs >0.75 s were assumed to be due to inattentiveness and were excluded from the averages. Three subjects with average RTs >0.5 s were excluded from the experiment.

Event-related potentials. The P300 waveform was measured during the performance of another behavioral task, the P300 task. This task also involved depressing the hand-held button in response to the red LED but not the green LED as described above. However, in the paradigm of the P300 task, the red LED was presented on 20% and the green LED on 80% of the trials. The intertrial interval was 3 s. Each block of trials continued until 14–18 trials were obtained without eye movement artifact. During the P300 task, subjects were instructed to count the number of times that the red LED was illuminated during each block of trials. Three replications of P300 blocks were obtained during each experimental period. Each P300 block was alternated with blocks of trials during which RT was measured as described above.

Event-related cerebral potentials were recorded during this P300-eliciting task. Cerebral responses to the frequently presented green LEDs and the infrequently presented red LEDs were averaged separately. Three replications of the waveforms were combined, resulting in average waveforms for each glucose condition based on 48 presentations of the red stimulus. Trials with RTs >0.75 s were not included in the averages, and neither were trials with eye movement or blink artifacts >500 μV.

Recordings were obtained from midline frontal (F_z), parietal (P_z), and occipital (O_z) scalp, referenced to linked mastoids (A_1–A_2). The ground electrode was placed on the vertex. Eye movement and blink artifacts were recorded bipolarly from electrodes placed lateral to and over the left canthus and lateral to and below the right canthus. Amplifier band pass was 0.1–30.0 Hz. The amplitude of each peak of the waveforms was measured relative to the average voltage between 0–50 ms. P300 latency was determined from the greatest positivity, unless two distinct and reliable peaks were evident (P3a, P3b). In this situation, the second peak was chosen, even though occasionally the P3a peak was of greater amplitude. To compare the P300 waveforms after presentation of auditory and visual stimuli, an additional nine volunteers were studied. During these studies, in addition to the visual stimuli described, an auditory P300 task that used

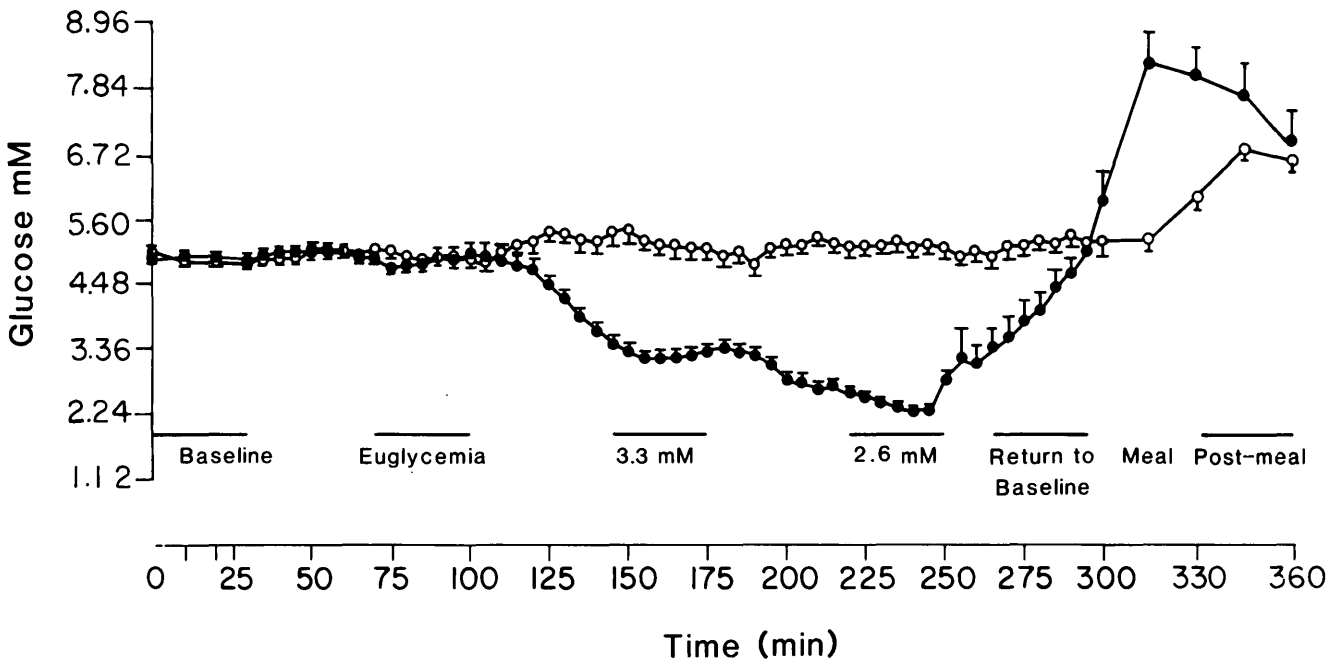

FIG. 1. Mean ± SE plasma glucose concentrations during hypoglycemic (●) and euglycemic (○) sessions. *Horizontal bars* signify time intervals during which experimental measurements were obtained. Subjects consumed high-carbohydrate meal from 300 to 330 min.

a 2-kHz rare tone and a 1-kHz frequent tone was used to obtain event-related potentials.

Statistical analysis. For each subject, results of the hypoglycemic clamp session were compared with the comparable block of the euglycemic clamp study. Repeated-measures analysis of variance was used to determine if RT, P300 latency, and the counterregulatory hormone response differed under the euglycemic and hypoglycemic conditions (12). Tukey's Studentized range test was used for post hoc comparisons.

RESULTS

Glucose levels. Changes in serum glucose during the hypoglycemic and euglycemic sessions are shown in Fig. 1. During the hypoglycemic session, baseline glucose of 5.00 ± 0.04 mM was similar to the level achieved during the euglycemic clamp portion of the same session (4.90 ± 0.06 mM). Glucose levels were then lowered sequentially to 3.30 ± 0.04 and 2.60 ± 0.05 mM. As glucose was infused intravenously to correct hypoglycemia, plasma glucose rose to a peak value of 5.4 ± 0.2 mM. After consumption of a high-carbohydrate meal, glucose rose to 7.6 ± 0.3 mM. During the 6-h euglycemic clamp session, plasma glucose was 5.10 ± 0.03 mM and rose to 6.5 ± 0.2 mM after consumption of the high-carbohydrate meal.

Visual event-related potentials. Representative waveforms obtained from a single subject are shown in Fig. 2. The cerebral response to the noncounted green stimuli for this subject contained a single parietal visual evoked potential negative peak with a latency of ~200 ms, with no subsequent peaks following it. In contrast, the responses to the counted red stimuli contained the same component, followed by a greater amplitude negative-positive-negative complex. The parietal distribution of the major positive peak at ~400 ms, coupled with its association to the counted stimuli only, indicate that this is the P300 cognitive event-related potential. The complex is not accompanied by significant activity in the eye-movement channel, indicating cerebral origin. Sim-

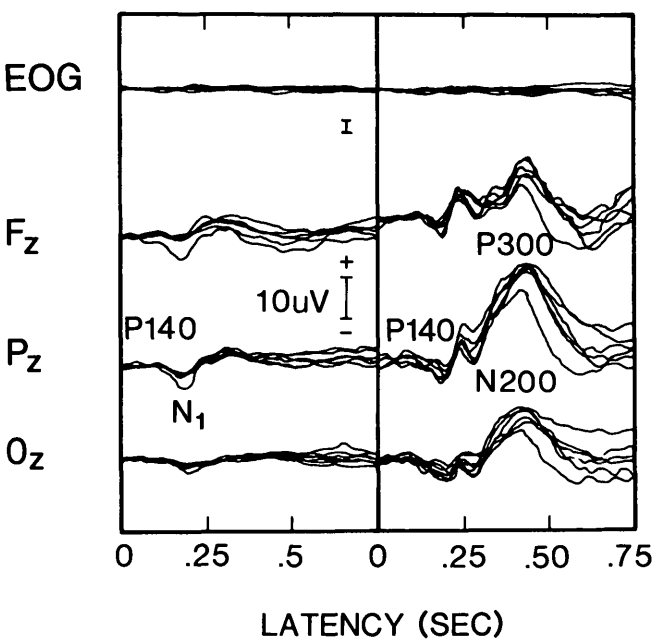

FIG. 2. Waveforms from frontal (F_z), parietal (P_z), and occipital (O_z) electrodes obtained from representative subject during euglycemic session. Each waveform represents electrical recordings from 3 trials when subject was presented with frequent stimulus (green light) depicted in *left panel* and rare stimulus (red light) depicted in *right panel*. Each of 6 experimental periods is superimposed. Subjects were instructed to press button and keep count of number of times rare stimulus was presented. Sensory evoked potential (P140, N_1) was present in response to both frequent and rare stimuli. P300 component (P3) was present only in response to rare stimulus. P300 component was greatest in amplitude at P_z lead. Simultaneous recording of electrooculogram (EOG) documents absence of artifact from eye movements.

ilar criteria were used to identify this component in the recordings of all subjects.

The effects of the reduction in plasma glucose on P300 are illustrated in Figs. 3 and 4 and Table 1. These waveforms represent the average responses of the 10 subjects under each glucose condition. Neither the amplitude nor the latency of the P300 waveform changed significantly during the euglycemic study (13,14). However, during the hypoglycemic study when blood glucose was lowered to 2.6 mM, the peak of P300 increased from a basal value of 410 ± 6 to 435 ± 11 ms. P300 latency was not significantly different from baseline at 3.3 mM, indicating that the threshold for changes in P300 due to hypoglycemia lies between 2.6 and 3.3 mM. When glucose was infused intravenously to reverse hypoglycemia, P300 latency remained prolonged by 49 ms above baseline ($P < 0.0001$). After consumption of the high-carbohydrate meal, P300 latency returned to baseline values. The reduction in P300 amplitude during the hypoglycemic study was not statistically significant. The early sensory P140 peak did not change in amplitude or latency. An increase in P300 latency during the hypoglycemic session was not observed in 2 subjects (Fig. 4).

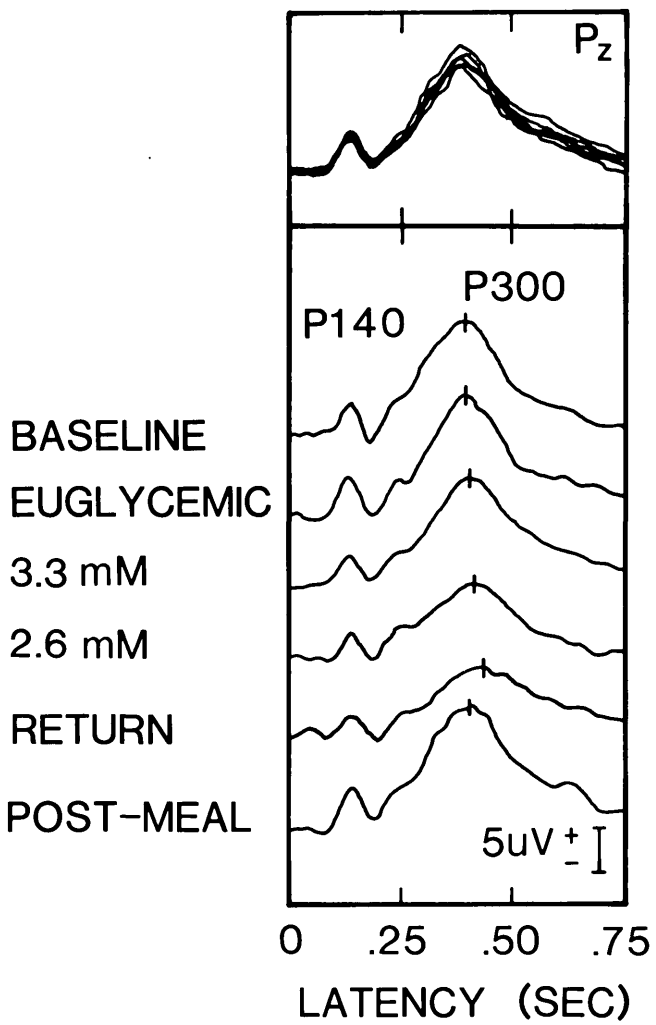

FIG. 3. P300 component from parietal (P_z) recordings of 10 subjects during euglycemic session (*top*) and hypoglycemic session (*bottom*) during each experimental period. P300 latency was constant throughout euglycemic session. During hypoglycemic session, P300 latency increased at glucose concentration of 2.6 mM, but largest increase in latency was seen during recovery of hypoglycemia, as blood glucose returned to baseline.

To determine whether the change of P300 latency during the 2.6-mM condition was due to the cumulative effect from the previous blood glucose level of 3.3 mM, three subjects who showed an increase in P300 latency at blood glucose levels of 2.6 mM were restudied under the same protocol, except that glucose levels were maintained at 3.3 mM for 150 min. None of these subjects showed an increase in P300 latency under this extended 3.3-mM clamp.

Auditory event-related potentials. Except for the often-described finding that the latency of P300 in response to auditory stimuli is less than P300 latency elicited by visual stimuli (15), the changes in auditory P300 showed trends similar to the above changes in visual P300 latency (Table 2). Baseline auditory P300 was 328 ms. Although the increase in response to 2.6 mM blood glucose did not reach statistical significance, a significant increase in auditory P300 latency was observed after intravenous glucose administration ($P < 0.0001$). After consumption of a high-carbohydrate meal, auditory P300 latency returned to baseline. P300 latency to visual stimuli increased by 34 ms over baseline at blood glucose levels of 2.6 mM ($P < 0.05$). As blood glucose levels returned to baseline, visual P300 latency increased to 49 ms above baseline ($P < 0.0001$). Neither the auditory nor the visual P300 showed a significant increase in latency when blood glucose was clamped at 3.3 mM. Two-way analysis of variance revealed that the interaction between glucose levels and sensory modality was not significant.

Reaction time. Like P300 latency, RT also increased in response to hypoglycemia, except for two subjects who exhibited no noticeable increase in latency (Fig. 5). The increases were statistically significant at 2.6 mM and persisted after intravenous glucose administration. The mean increase in RT was not due to a change in the distribution of late responses, which might be expected if arousal levels changed during the task or if subjects became inattentive to the task during the hypoglycemic blocks of trials (16). Histograms constructed from the RTs of all 10 subjects during portions of the hypoglycemic session demonstrate that the mean increase in RT latency during the hypoglycemic study was clearly not due to the mild increase in late responses under that condition but was rather due to a general slowing of RT (Fig. 6). Similar increases were observed in the RT task performed during P300 acquisition (Table 1). RT showed no significant change in the euglycemic study (Table 1). During the hypoglycemic study, RTs measured in the P300 task increased 39 ms above baseline at blood glucose levels of 2.5 mM ($P < 0.01$) and an additional 23 ms as glucose was infused intravenously to raise glucose levels to baseline ($P < 0.0001$). The results obtained from the RT paradigm modeled after Herold et al. (17) had a baseline RT of 384 ms, which increased by 39 ms at glucose levels of 2.6 mM; this change was not statistically significant ($P < 0.06$). When glucose was infused to correct the hypoglycemia, RT increased by 62 ms over baseline ($P < 0.0001$). After consumption of a high-carbohydrate diet, RT showed no statistically significant difference from baseline. The correlation between P300 latency and RT from the hypoglyce-

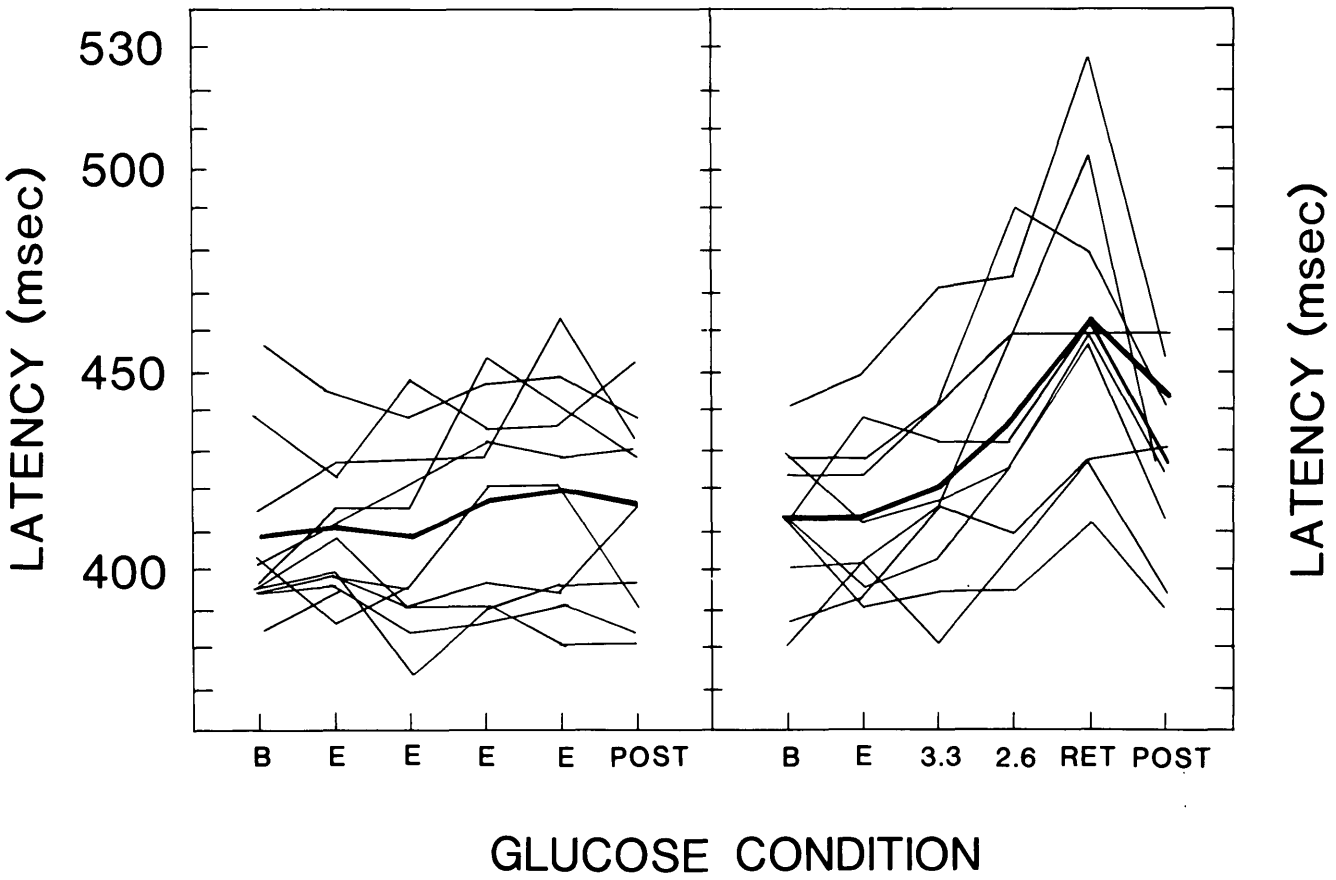

FIG. 4. P300 latency recordings for 10 experimental subjects during euglycemic (*left panel*) and hypoglycemic studies (*right panel*). B, baseline; E, euglycemia; 3.3, 3.3 mM glucose; 2.6, 2.6 mM glucose; RET, return to baseline; POST, postmeal. Individual *thin lines*, recordings from individual subjects. *Thick line*, mean values across group.

mic session was $r = 0.44$ ($P < 0.0001$). This result is consistent with previous results obtained by Kutas et al. (5).

Count errors and late responses. The number of count errors was calculated as a percentage of the total counts for each condition. In both the euglycemic and hypoglycemic studies, the average error rates were ≤1.1% of the total count. This result implies that this simple memory task was not strongly affected at the level of hypoglycemia used in this experiment.

During the euglycemic session, the percentage of late or absent responses was <1.1%. During the hypoglycemic session at baseline, euglycemic, and 3.3-mM glucose levels, the late response rate was also <1.1%. At glucose levels of 2.6 mM, the late response rate trended upward to 4.4% (NS), and after correction of hypoglycemia with intravenous glucose, the late response rate rose to 5.7% ($P < 0.001$). After consumption of a high-carbohydrate meal, the rate decreased to 1.4%. Arousal or attentiveness was only mildly affected during the hypoglycemic session, because a response rate >94% correct was maintained under all conditions (18).

Symptom scores. During the euglycemic session, none of the subjects reported any symptoms. During the hypoglycemic session, the subjects reported no symptoms at baseline, euglycemia, or at the 3.3-mM clamp level. However, when plasma glucose was lowered to 2.6 mM, all subjects

TABLE 1
Changes in visual P300 latency and reaction time (RT) during euglycemic and hypoglycemic studies

	Euglycemic			Hypoglycemic		
Time (min)	P300 latency (ms)	RT (ms)	Glucose (mM)	P300 latency (ms)	RT (ms)	Glucose (mM)
0–30	406 ± 7	365 ± 11	5.00 ± 0.03	410 ± 6	365 ± 7	5.00 ± 0.04
70–100	411 ± 3	375 ± 11	5.00 ± 0.05	411 ± 6	362 ± 9	4.90 ± 0.06
145–175	406 ± 7	363 ± 9	5.30 ± 0.06	418 ± 8	361 ± 10	3.30 ± 0.04
220–250	415 ± 7	359 ± 11	5.20 ± 0.04	435 ± 11*	413 ± 19†	2.60 ± 0.05
265–300	417 ± 9	354 ± 9	5.30 ± 0.60‡	459 ± 12§	432 ± 16§	5.40 ± 0.20‡
330–360	412 ± 8	351 ± 11	6.50 ± 0.20	420 ± 7	375 ± 10	7.60 ± 0.30

*$P < 0.05$, †$P < 0.01$, §$P < 0.0001$, vs. baseline (0–30 min). All other comparisons not significant.
‡Plasma glucose at 295 min.

TABLE 2
Changes in P300 latency during auditory-visual paradigm

Time (min)	Auditory P300 (ms)	Visual P300 (ms)	Glucose (mM)
0–30	328 ± 6	365 ± 8	5.20 ± 0.06
70–100	327 ± 6	369 ± 7	5.30 ± 0.07
145–175	334 ± 5	377 ± 7	3.50 ± 0.04
220–250	344 ± 6	399 ± 7*	2.50 ± 0.03
265–300	353 ± 6†	414 ±10†	5.20 ± 0.20‡
330–360	329 ± 6	376 ± 8	8.10 ± 0.40

*$P < 0.05$, †$P < 0.0001$, vs. baseline (0–30 min). All other comparisons not signficant.
‡Plasma glucose at 295 min.

reported diaphoresis, palpitations, and difficulty thinking and concentrating. Blurred vision was less common and was reported by only 2 of the 10 subjects. These symptoms gradually disappeared when plasma glucose was raised to baseline levels by the administration of intravenous glucose. As baseline glucose was achieved, only 2 subjects reported experiencing difficulty thinking or concentrating. After consumption of a high-carbohydrate meal, no subjects reported hypoglycemic symptoms.

Counterregulatory hormones. As blood glucose levels were lowered to 3.3 mM, counterregulatory hormones did not significantly increase from their basal levels. At 3.3 mM, cortisol levels were 230 ± 30 nM, plasma epinephrine levels were 1400 ± 450 pM, glucagon levels were 80 ± 3 ng/L, and growth hormone levels were 3 ± 1 μg/L. However, as blood glucose levels of 2.6 mM were achieved, cortisol levels rose from a baseline of 230 ± 39 to 600 ± 33 nM ($P < 0.0001$), plasma epinephrine increased from 810 ± 240 to 5700 ± 870 pM ($P < 0.001$), glucagon increased from 90 ± 6 to 177 ± 18 ng/L ($P < 0.01$), and growth hormone increased from 0.2 ± 0.1 to 34 ± 15 μg/L ($P < 0.05$). As glucose was infused to return plasma glucose to baseline, the counterregulatory response decreased, with the exception of cortisol, which remained elevated.

DISCUSSION

This study demonstrates that the threshold for cognitive dysfunction defined by changes in the latency of P300 lies between 3.3 and 2.6 mM glucose for most healthy subjects. This threshold is consistent with studies that use neuropsychological testing (19–21) and EEGs (22). Although the increase in P300 latency was statistically significant for the group as a whole, some variability was observed between subjects. Two of 10 subjects showed no increase in P300 latency at plasma glucose concentrations of 2.6 mM. For the remaining 8 subjects, increases in P300 latency varied from

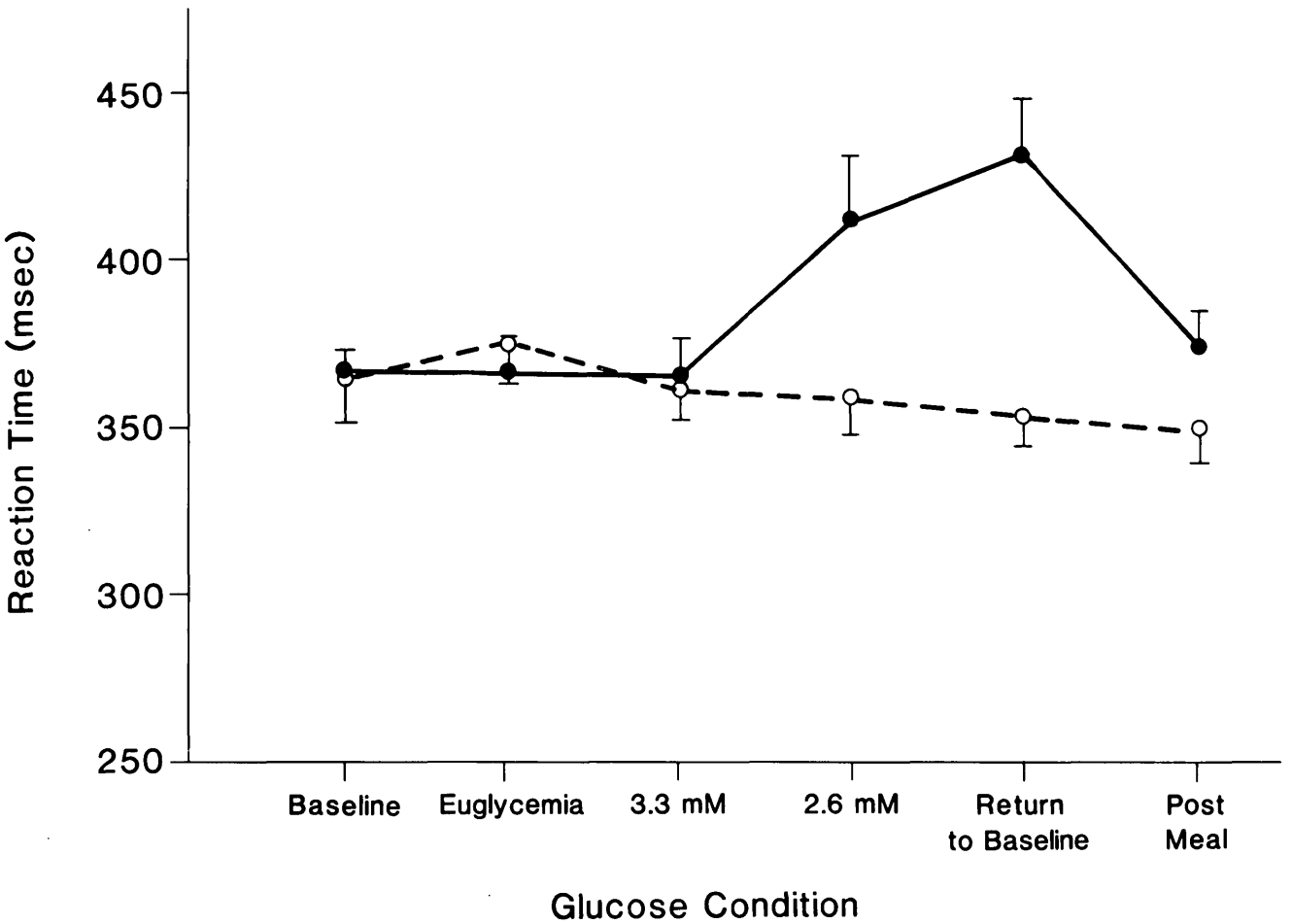

FIG. 5. Mean ± SE reaction time recorded during P300 task under euglycemic (○) and hypoglycemic (●) conditions. $P < 0.01$ between conditions at 2.6 mM glucose; $P < 0.0001$ at return to baseline.

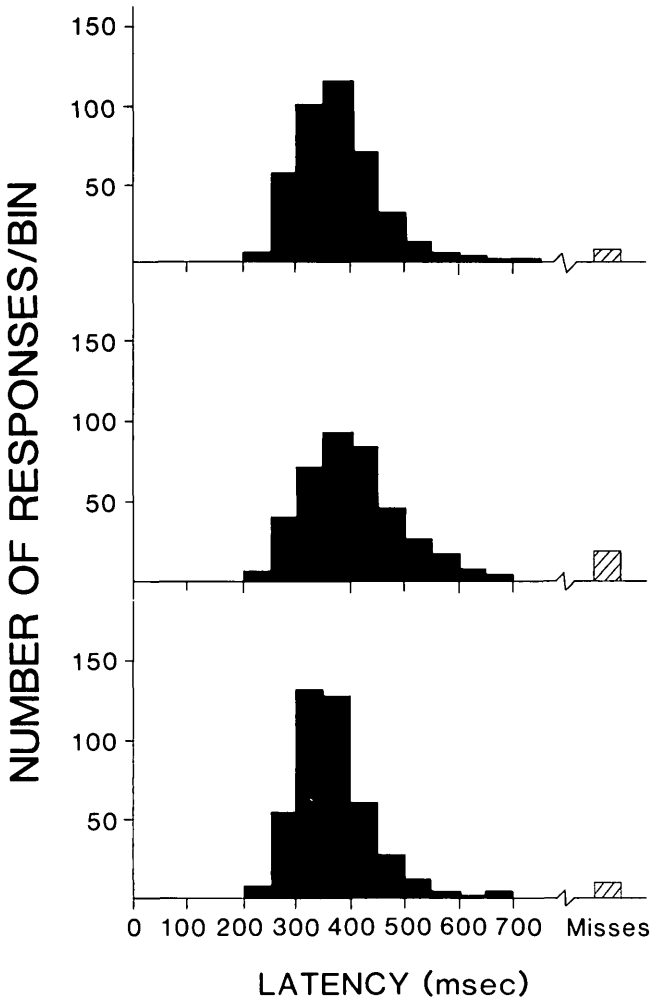

FIG. 6. Reaction-time (RT) histograms during euglycemic (*top*), 2.6 mM glucose (*middle*), and postmeal (*bottom*) portions of hypoglycemic study. Although there was slight increase in number of misses at 2.6 mM glucose, general shape of RT distribution was maintained.

15 to 64 ms. The physiological basis for this variability is not known but has been previously observed in studies of RT during hypoglycemia (17).

The cognitive dysfunction induced by hypoglycemia did not recover immediately on elevation of plasma glucose with intravenous glucose. This observation is probably due to a continued deterioration in response to the 2.6-mM glucose clamp. After the induction of hypoglycemia, the prolongation of P300 persisted a maximum of 30 min after plasma glucose had been raised to 5.4 mM. P300 returned to baseline levels only after ingestion of a carbohydrate-rich meal. This provides objective support for the bedside observation that recovery of diabetic patients to normal cognitive function may lag behind restoration of plasma glucose levels with exogenous glucose. Patients may require at least 45–75 min after even mild hypoglycemia before they can adequately perform routine tasks. The period required for full recovery of cerebral function may be considerably longer if hypoglycemia is severe and/or of long duration.

Several techniques for evaluating cerebral function during hypoglycemia have been used. Holmes et al. (19,20) used neuropsychological testing and found slowed math recall and impaired performance of a visual RT task for patients with type I diabetes mellitus at blood glucose levels of 3.1–3.3 mM. By use of neuropsychological testing at discrete glucose intervals with type I diabetic patients, Pramming et al. (21) found that test scores deteriorated for 12 of 16 subjects at plasma glucose levels of 3 mM. He expanded his work to include EEG recordings during insulin-induced hypoglycemia and found that the EEG did not significantly change until plasma glucose concentrations were <2 mM (22). Herold et al. (17) studied the effects of reductions in plasma glucose concentrations on RT to a visual stimulus. RT was shown to be an objective reproducible measure of cerebral dysfunction during insulin-induced hypoglycemia.

DeFeo et al. (23) reported that the latency of P300 to an auditory stimulus was prolonged at a level of 4 mM with reductions of baseline plasma glucose concentration as modest as 0.84 mM. This study failed to replicate these findings, and the data are consistent with the conclusion that plasma glucose must be reduced to <3.3 mM before significant changes in cognitive function are observed. Even when plasma glucose was clamped at 3.3 mM for >2 h, the P300 latency was not altered. The differences between the findings of DeFeo et al. and the results of this study cannot be ascribed to differential sensitivity of visual and auditory P300.

Our data also provide insight into the specific cerebral cortical functions involved in the dysfunction induced by hypoglycemia and suggest that decision processing is predominantly affected. Sensory processes do not appear to be altered by hypoglycemia, because no systematic changes were observed in the latency of P140, the component associated with initial sensory processing in the visual and/or parietal cortex. This finding was also observed by Gallai et al. (24) during mild hypoglycemia. Brain stem auditory evoked potentials were obtained in a subject in whom P300 was delayed, but no changes in peaks I–V of these potentials were observed during the hypoglycemic manipulation.

Similarly, hypoglycemia of the levels achieved in this study does not appear to affect motor processes. The mean changes in P300 latency paralleled those of RT, suggesting motor processes related to the RT task were not the source of the delays (15). The latency of P300 is believed to reflect the duration of sensory processing and stimulus evaluation but not subsequent response organization and execution (3–5). Because the delays in event-related potentials were manifested after the sensory components but before the P300 component, the data suggest a slowing of brain processes related to decision making. Finally, the mild increases in late responses and the lack of a change in the shape of the distributions of RT suggest that the cognitive slowing observed in this study was not due to decreased arousal or lapses of attention.

In conclusion, the P300 component of event-related cerebral potentials, an electrophysiological correlate of cognitive decision-making processes, is a sensitive index of cognitive dysfunction during insulin-induced hypoglycemia, comparable with RT. The plasma glucose level at which cognitive dysfunction occurs in most nondiabetic subjects is between 2.6 and 3.3 mM. Individual thresholds to hypoglycemia differ, with some nondiabetic subjects exhibiting no cognitive deterioration at these levels. The slowing of ce-

rebral function persisted as euglycemia was achieved and after hypoglycemic symptoms had disappeared. The basis of the individual differences in susceptibility to hypoglycemia are not well understood. A better understanding of individual differences may provide insight into identifying patients who may have a greater risk of experiencing hypoglycemia-induced cognitive dysfunction.

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