

Adaptation of Cognitive Function to Hypoglycemia in Healthy Men

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OBJECTIVE — Antecedent hypoglycemia reduces hypoglycemic counterregulation and symptoms, thereby provoking the hypoglycemia unawareness syndrome. The effects of antecedent hypoglycemia on hypoglycemia-induced cognitive dysfunction are less well established.

RESEARCH DESIGN AND METHODS — To determine whether antecedent hypoglycemia also reduces hypoglycemic cognitive dysfunction, we performed stepwise hypoglycemic clamp experiments (4.1, 3.6, 3.1, and 2.6 mmol/l) during a 6-h period in 30 young healthy men. A total of 15 subjects additionally received a 2.5-h antecedent hypoglycemic clamp (3.1 mmol/l) on the preceding day (prior-hypo group), whereas the other 15 subjects did not (control group). Cognitive function was assessed by auditory-evoked brain potentials (AEBPs) and reaction time during a vigilance task and short-term memory recall. Tests were performed during the stepwise hypoglycemic clamp at baseline and at each hypoglycemic plateau.

RESULTS — In both groups, performance on all measures of cognitive function deteriorated during stepwise hypoglycemia (all $P < 0.01$). However, after antecedent hypoglycemia, the hypoglycemia-induced decrease in the amplitude of the P3 of the AEBP was distinctly reduced compared with the control condition ($P < 0.05$). Also, short-term memory performance was less impaired in the prior-hypo group than in the control group ($P < 0.005$), and a minor hypoglycemic impairment of reaction time ($P < 0.05$) was evident in the prior-hypo group.

CONCLUSIONS — Data provide evidence that a single episode of mild antecedent hypoglycemia (3.1 mmol/l) attenuates several aspects of cognitive dysfunction during subsequent hypoglycemia 18–24 h later.

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Hypoglycemia is the limiting factor in the management of type 1 diabetes (1). Tight glycemic control as a result of intensive insulin therapy has been shown to be accompanied by a 3-fold increase in the risk of severe hypoglycemia (2). Although specific treatment programs may help to decrease the risk of hypoglycemia (3), hypoglycemia still constitutes a severe problem for many patients with type 1 diabetes. Patients with well-controlled diabetes frequently

show a reduced counterregulatory and symptomatic response to hypoglycemia that is often referred to as the “hypoglycemia unawareness syndrome” (4). Hypoglycemia itself seems to be the major factor in the pathogenesis of the syndrome because antecedent hypoglycemia has been shown to reduce hypoglycemic counterregulation and symptoms in type 1 diabetic patients (5–7) and in healthy subjects (8–16). However, unawareness may also result from a direct

impairing influence of hypoglycemia on neurocognitive function (17–20). The effect of antecedent hypoglycemia on hypoglycemic cognitive dysfunction has been discussed controversially thus far (21,22). Several studies (6,7,14,23) failed to detect any significant effects, whereas others (15,24–26) indicated a preserving influence of antecedent hypoglycemia on cognitive function. The inconsistency appears to be related to methodical differences pertaining to the heterogeneity of the subjects studied, the small size of subject samples, and the cognitive function tests used. Some of these problems were overcome in the present study, which assessed the effect of a single episode of antecedent hypoglycemia on cognitive dysfunction during subsequent hypoglycemia in healthy men. We tested the hypothesis that antecedent hypoglycemia diminishes cognitive dysfunction during subsequent hypoglycemia. Indicators of cognitive functions were auditory-evoked brain potentials (AEBPs) and reaction time during a vigilance task and short-term memory recall. Because psychological factors such as fatigue or anxiety (22) may confound cognitive function testing during hypoglycemic clamp experiments, we also assessed the state of arousal by questionnaire and with physiological parameters such as blood pressure and heart rate.

RESEARCH DESIGN AND METHODS

Participants

A total of 30 healthy men participated in the experiments (means \pm SEM, 26 ± 1 years of age; BMI 23.1 ± 0.6 kg/m²). Exclusion criteria were chronic or acute illness, taking medication of any kind, obesity, smoking, alcohol or drug abuse, and diabetes or hypertension in first-degree relatives. Each volunteer gave written informed consent, and the study was approved by the local ethics committee. All volunteers were requested to abstain from alcohol, not to perform any kind of exhausting physical activity, and to go to bed no later than 10:00 P.M. on the day before the experiments.

Procedure

Stepwise hypoglycemic clamp experiments during a 6-h period were per-

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Abbreviations: AEBP, auditory-evoked brain potential; ANCOVA, analysis of covariance; Cz, central electrode location; EEG, electroencephalogram; EOG, electrooculogram; Fz, frontal electrode location; prior-hypo group, subjects who received a 2.5-h antecedent hypoglycemic clamp on the preceding day; Pz, parietal electrode location.

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

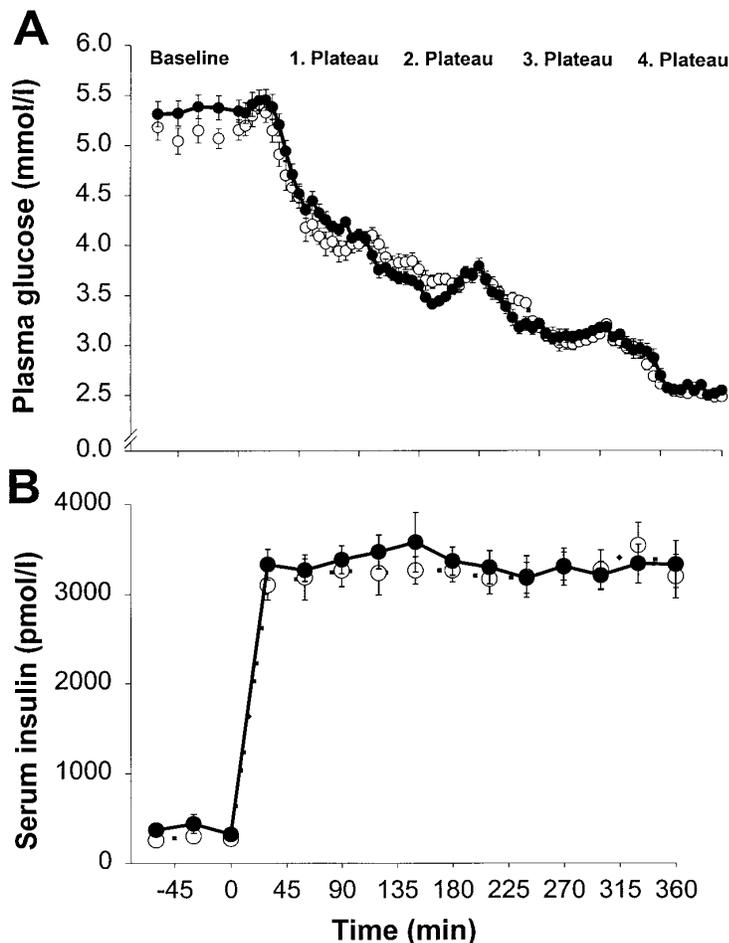


Figure 1—Means \pm SEM concentration of plasma glucose (A) and serum insulin (B) in the prior-hypo group (●) and the control group (○) during baseline and stepwise hypoglycemic clamp studies.

formed in 30 subjects randomly allocated to 2 groups. One group additionally underwent an antecedent hypoglycemic clamp that lasted 2.5 h on the day preceding the stepwise hypoglycemia (prior-hypo group), whereas the other 15 subjects did not undergo the clamp study (control group). A moderate antecedent hypoglycemic level of ~ 3.1 mmol/l was chosen because, under this condition, antecedent hypoglycemia per se is not expected to induce acute cognitive disturbances that may interfere with the effects of subsequent hypoglycemia (27–30).

On the day of the antecedent hypoglycemic clamp study, the subjects in the prior-hypo group reported to the medical research unit at 1:30 P.M. They were instructed not to have breakfast on this day and to abstain from eating until the end of the clamp study. The experiments took place in a sound-attenuated room with the subjects sitting with their trunks in an

almost upright position ($\sim 60^\circ$) and their legs in a horizontal position on a bed. A cannula was inserted into a vein on the back of the hand, which was placed in a heated box (50 – 55°C) to obtain arterialized venous blood. A second cannula was inserted into an antecubital vein on the contralateral arm. Both cannulas were connected to long thin tubes that enabled blood sampling and adjustment of the rate of dextrose infusion from an adjacent room without being noticed by the subject. At 2:00 P.M., infusion of insulin (H-insulin; Hoechst, Frankfurt, Germany) began at a continuous rate of $1.5 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Plasma glucose levels (Beckman Glucose Analyzer; Beckman Instruments, Munich, Germany) were measured every 5 min, and a variable infusion of 20% dextrose solution was adjusted so that plasma glucose levels were held constant at ~ 3.1 mmol/l. Neurocognitive tests were not performed during the antecedent hypoglycemic clamp.

On the day of the stepwise hypoglycemic clamp study, all subjects reported to the medical research unit at 8:00 A.M. after an overnight fast of at least 10 h. The setting of the stepwise hypoglycemic clamps was the same as that of the antecedent hypoglycemic clamps. After a 1-h baseline period, insulin was infused at a continuous rate of $1.5 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for the subsequent 6 h. Arterialized blood was drawn at 5-min intervals to measure plasma glucose concentration. A 20% dextrose solution was simultaneously infused at a variable rate to control plasma glucose levels. Plasma glucose levels were reduced in a stepwise manner to achieve 4 plateaus of ~ 4.1 , 3.6, 3.1, and 2.6 mmol/l. Each plateau was maintained for 45 min, and the next lower plateau was induced gradually within the next 45 min. Standard cognitive tests were performed at each of the hypoglycemic plateaus.

AEBPs and reaction time

AEBPs indexing different stages of the brain's stimulus processing and reaction times were recorded while the subject performed a vigilance task (oddball paradigm). The task required the subject to detect target pips (1,200 Hz, duration 60 ms, intensity 64 decibel sound pressure level, probability 0.1) that were randomly interspersed among frequent standard pips of lower pitch (800 Hz), and the task contained ~ 400 pips. Tone pips were presented binaurally through headphones with an interstimulus interval randomly varying between 1,000 and 3,000 ms (mean 2,000). The subject was instructed to press a button with the thumb of the dominant hand as quickly as possible whenever he recognized a target pip (reaction time). To avoid electroencephalogram (EEG) artifacts, the subject was asked to fixate his eyes on a centrally located dot and not to blink too often during task performance. Analyses of the AEBP focused on the P3 component (also termed "P300"), which is a large potential component evoked by the task-relevant target pips of the vigilance task. It typically peaks at ~ 350 – 450 ms post-stimulus over parietal cortical regions. The P3 is considered an indicator of the target processing within working memory (31), although the psychological significance of P3 is a matter of ongoing debate (32,33). For AEBP assessment, the EEG (5-s time constant, 70-Hz/12-dB high-frequency roll off, 0.045-Hz/6-dB low-frequency roll off) was recorded continuously from frontal (Fz), central (Cz), and parietal (Pz) electrode loca-

tions referenced to linked electrodes attached to the earlobes. An electrode at frontal parietal electrode location served as a baseline. For artifact recognition, the vertical EOG was monitored. Nonpolarizable silver–silver chloride electrodes 16 mm in diameter were used. EEG and EOG signals were amplified by a Nihon Kohden Neurofax 4421 G polygraph (Nihon Kohden, Japan) and digitized (CED 1401; Cambridge Electronic Design, Cambridge, U.K.) with a sampling rate of 385 Hz for off-line averaging of AEBPs. As previously described (34), data analysis of the recorded AEBPs calculated the latency and baseline-to-peak amplitude of the P3 component after the task-relevant target pip. P3 was defined with regard to the maximum positive amplitude from 280 to 740 ms poststimulus.

Short-term memory task

Short-term memory testing consisted of the consecutive presentation of 2 different word lists, each containing 15 words. The words belonged to 3 semantic categories: neutral words like “tree” and “field,” food-related words like “ham” and “eggs,” and emotional words like “mother” and “friend.” To enable repeated testing, 10 different lists were formed from a pool of words with each list including 5 words from each semantic category in random order. Words were presented orally at a rate of 1 word per second. After each list and a subsequent break of 1 min, the subject was required to verbally recall all of the words that he remembered from the preceding list within 1 min. The number of words correctly recalled at each testing was determined and summed across the 2 lists for all words presented as well as separately for each semantic category. Also, the number of false answers was determined (i.e., words that had been presented in a prior list or were never presented). However, the number of such errors was small, and respective analyses did not yield any conclusive information. Therefore, these data are not presented herein.

Indicators of the arousal state

A symptom and mood questionnaire was administered every 15 min. Subjects scored from 0 (none) to 4 (severe) on each of the following symptoms and moods: bodily discomfort, inner tension, anxiety, ability to concentrate, annoyance, fatigue, and excitability. The rating scores were averaged across the baseline phase and each of the hypo-

glycemic plateaus, respectively. Blood pressure and heart rate were measured automatically by a BC 40 (Bose-Prestige Automatic; Bosch und Sohn, Jungingen, Germany), which simulated the Riva-Rocci procedure at baseline and

each of the hypoglycemic plateaus before the cognitive tests.

Hormone measurements

Blood samples for measurements of counterregulatory hormones (cortisol,

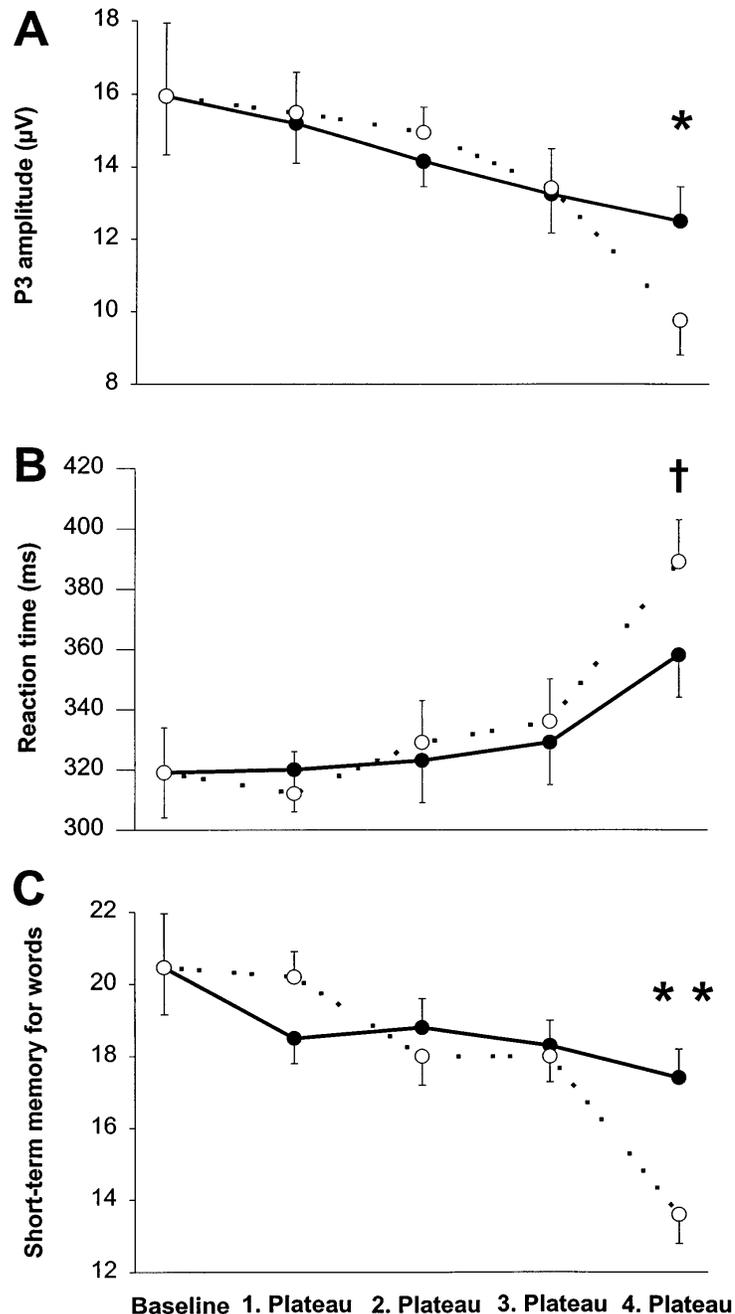


Figure 2—Amplitude of the P3 component of the AEBP recorded at Pz (A), reaction time to targets in an auditory vigilance task (B), and short-term memory recall (C) defined by the number of words recalled correctly from 2 lists, each of 15 words, in the prior-hypo group (●) and in the control group (○) during stepwise hypoglycemic clamp studies. Data are means \pm SEM adjusted for baseline as derived from ANCOVA. * $P < 0.05$, † $P < 0.1$, and ** $P < 0.005$ for differences between both experimental conditions in post hoc pairwise contrast.

Hypoglycemia and cognitive function

Table 1— Self-rated symptom and mood scores, blood pressure, heart rate, and counterregulatory hormone concentrations at baseline and the 4 hypoglycemic plateaus

Variable	Baseline	Plateau 1 (4.1 mmol/l)	Plateau 2 (3.6 mmol/l)	Plateau 3 (3.1 mmol/l)	Plateau 4 (2.6 mmol/l)	P (plasma glucose effect)	P (group effect)	P (group × plasma glucose interaction)
Bodily discomfort								
Prior-hypo	0.43 ± 0.14	0.50 ± 0.16	0.48 ± 0.15	0.95 ± 0.20	1.42 ± 0.26	<0.001	0.41	0.56
Control	0.27 ± 0.08	0.35 ± 0.15	0.48 ± 0.19	0.87 ± 0.25	1.53 ± 0.30			
Inner tension								
Prior-hypo	0.32 ± 0.11	0.38 ± 0.13	0.35 ± 0.13	0.77 ± 0.16	1.25 ± 0.20	<0.001	0.44	0.39
Control	0.27 ± 0.13	0.30 ± 0.13	0.45 ± 0.17	0.80 ± 0.23	1.35 ± 0.23			
Anxiety								
Prior-hypo	0.04 ± 0.03	0.02 ± 0.02	0.07 ± 0.05	0.07 ± 0.07	0.25 ± 0.13	0.33	0.58	0.18
Control	0.11 ± 0.07	0.10 ± 0.07	0.08 ± 0.08	0.15 ± 0.11	0.22 ± 0.12			
Concentration								
Prior-hypo	2.37 ± 0.23	2.07 ± 0.20	2.02 ± 0.12	1.92 ± 0.16	1.62 ± 0.18	0.39	0.76	0.43
Control	2.33 ± 0.18	2.30 ± 0.19	2.07 ± 0.18	1.88 ± 0.20	1.48 ± 0.17			
Annoyance								
Prior-hypo	0.12 ± 0.07	0.10 ± 0.07	0.10 ± 0.07	0.18 ± 0.11	0.20 ± 0.11	0.54	0.45	0.15
Control	0.09 ± 0.04	0.03 ± 0.03	0.12 ± 0.10	0.23 ± 0.16	0.38 ± 0.19			
Fatigue								
Prior-hypo	0.99 ± 0.22	1.10 ± 0.20	1.22 ± 0.23	1.15 ± 0.19	0.98 ± 0.20	0.99	0.37	0.31
Control	1.27 ± 0.18	1.38 ± 0.22	1.38 ± 0.23	1.50 ± 0.22	1.66 ± 0.31			
Excitability								
Prior-hypo	1.47 ± 0.26	1.38 ± 0.23	1.32 ± 0.20	1.20 ± 0.19	1.08 ± 0.19	0.72	0.48	0.87
Control	1.09 ± 0.22	1.05 ± 0.21	0.92 ± 0.22	0.85 ± 0.18	0.82 ± 0.18			
Heart rate (bpm)								
Prior-hypo	66.2 ± 3.7	66.3 ± 3.5	63.5 ± 1.8	68.6 ± 2.2	69.1 ± 2.5	<0.05	0.51	0.66
Control	62.7 ± 1.4	64.3 ± 1.5	64.1 ± 1.4	66.4 ± 2.0	66.3 ± 1.9			
Systolic blood pressure (mmHg)								
Prior-hypo	126.5 ± 2.0	125.5 ± 2.8	130.3 ± 3.4	132.0 ± 2.9	138.0 ± 4.4	<0.001	0.22	0.93
Control	123.0 ± 3.1	121.7 ± 2.2	124.3 ± 2.8	127.2 ± 3.0	132.3 ± 4.0			
Diastolic blood pressure (mmHg)								
Prior-hypo	78.8 ± 2.2	78.4 ± 2.8	76.8 ± 3.2	71.8 ± 2.6	70.4 ± 2.8	<0.001	0.23	0.79
Control	75.4 ± 2.0	72.1 ± 1.8	72.1 ± 1.8	67.1 ± 1.8	67.3 ± 0.2			
Cortisol (nmol/l)								
Prior-hypo	207 ± 15	267 ± 37	250 ± 24	352 ± 35	528 ± 35	<0.001	<0.05	0.06
Control	211 ± 24	253 ± 27	349 ± 38	454 ± 37	660 ± 34			
Growth hormone (µg/l)								
Prior-hypo	1.0 ± 0.1	1.7 ± 0.6	6.9 ± 2.3	12.6 ± 1.9	19.7 ± 2.5	<0.001	<0.05	0.06
Control	1.0 ± 0.1	2.4 ± 0.7	9.5 ± 2.5	19.5 ± 2.5	29.1 ± 2.1			
Epinephrine (pmol/l)								
Prior-hypo	153 ± 27	296 ± 81	661 ± 99	1,763 ± 295	3,610 ± 496	<0.001	<0.05	<0.05
Control	128 ± 18	460 ± 159	1,504 ± 386	2,655 ± 573	5,376 ± 886			
Norepinephrine (nmol/l)								
Prior-hypo	1.15 ± 0.14	1.30 ± 0.13	1.42 ± 0.15	1.50 ± 0.11	1.94 ± 0.15	<0.001	<0.005	<0.05
Control	1.07 ± 0.14	1.29 ± 0.16	1.59 ± 0.15	1.95 ± 0.24	2.62 ± 0.30			

Data are means ± SEM, unless indicated otherwise. Baseline values of all measurements did not differ between the prior-hypo and control group and served as covariates in the ANCOVAs.

growth hormone, epinephrine, and norepinephrine) were drawn at baseline and at the end of the 4 hypoglycemic plateaus (90, 180, 270, and 360 min) of the hypoglycemic clamp. Blood samples for insulin measurements were drawn every 30 min. Hormone concentrations were measured as previously described (35).

Statistical analysis

Data are means ± SEM. Baseline values of all measurements were compared between the 2 groups by unpaired Student's *t* test. Analysis of covariance (ANCOVA) for repeated measurements was performed to detect effects of plasma glucose and antecedent hypoglycemia, including the factors of

plasma glucose (including the 4 glycemic plateaus) and group (prior-hypo vs. control) with baseline values serving as covariates. Only when main effects for the group factor or the group × plasma glucose interaction reached significance (*P* < 0.05) was post hoc analysis performed by ANCOVA at each of the glycemic plateaus. Also, measures of per-

formance on cognitive function tests, self-ratings, and counterregulatory hormones at the final hypoglycemic plateau were expressed as the difference from baseline. These difference values were subsequently subjected to stepwise forward multiple linear regression analysis with the changes in performance on cognitive function tests as dependent variables to determine their dependence on changes in self-ratings and counterregulatory hormones.

RESULTS

Glucose and insulin levels

During the antecedent hypoglycemic clamp, plasma glucose levels decreased to a steady-state level of 3.1 ± 0.1 mmol/l within the first 30 min of insulin infusion. This level was maintained for 2 h until the end of the clamp (data not shown). During the stepwise hypoglycemic clamp, plasma glucose levels decreased and serum insulin levels increased as expected with the time course of changes closely comparable between both groups (Fig. 1).

AEBP and reaction time

In both groups, amplitude of the P3 component significantly decreased during the stepwise hypoglycemic clamp (effect of plasma glucose across all electrode sites, $P < 0.01$). However, a significant group \times plasma glucose interaction effect ($P < 0.05$) was evident, which indicates that the decrease in P3 amplitude during the clamp was distinctly smaller in the prior-hypo group than in the control group. Although the effects did not interact with topography, separate comparisons for each electrode site indicated the preserving effect of antecedent hypoglycemia on P3 amplitude to reach significance at Pz ($P < 0.05$) (Fig. 2A) and at Cz ($P < 0.05$) but not at Fz ($P = 0.36$).

Similarly, the increase in P3 latency observed in both groups with progression of hypoglycemia was less pronounced in the prior-hypo group than in the control group. Overall ANCOVA indicated significance for the group \times plasma glucose interaction ($P < 0.005$) independent of topography. Separate comparisons at each electrode site indicated significance for this effect at Fz (13.4 ± 11.1 vs. 56.3 ± 8.6 ms; $P < 0.005$ for comparison at the last hypoglycemic plateau) and at Cz (12.0 ± 12.7 vs. 45.3 ± 8.0 ms; $P < 0.05$ for comparison at the last hypoglycemic plateau).

Reaction time to the target pips of the oddball task also increased in both groups

Table 2—Correlations between the changes (plateau 4 – baseline) in performance on cognitive function tests, self-rated symptom and mood scores, and counterregulatory hormones

	Δ P3 amplitude (at Pz)	Δ P3 latency (at Pz)	Δ Reaction time	Δ Word recall
Δ Concentration	-0.06	0.42*	-0.42*	0.25
Δ Fatigue	-0.17	0.05	0.58†	-0.39*
Δ Cortisol	-0.12	0.31	0.39*	-0.57†
Δ Growth hormone	-0.30	0.32	0.23	-0.32
Δ Epinephrine	-0.19	0.53‡	0.14	-0.49§
Δ Norepinephrine	-0.02	0.33	0.09	-0.35

Data are correlation coefficients. * $P < 0.05$; † $P < 0.001$; ‡ $P < 0.005$; § $P < 0.01$. Correlations between changes in performance on cognitive function tests and the other self-rated symptom and mood scores were not significant.

during hypoglycemia (effect of plasma glucose, $P < 0.001$). Again, a significant group \times plasma glucose interaction effect ($P < 0.05$) (Fig. 2B) indicated that, at the lowest hypoglycemic plateau, reaction time was less prolonged after the antecedent hypoglycemia than after the control condition (358.2 ± 13.4 vs. 389.2 ± 11.2 ms; $P = 0.07$).

Short-term memory recall

During the stepwise hypoglycemic clamp, recall performance deteriorated in both groups (effect of plasma glucose, $P < 0.001$), with this effect depending also on the presence of antecedent hypoglycemia ($P < 0.005$ for group \times plasma glucose interaction) (Fig. 2C). At the lowest hypoglycemic plateau, subjects in the prior-hypo group remembered on average almost 4 words more than subjects in the control group (17.4 ± 0.8 vs. 13.6 ± 0.8 ; $P < 0.005$). Overall, ANCOVA did not indicate a significant difference in word categories. In a separate analysis of the different word categories, the difference between experimental groups reached significance for recall of emotional words (6.2 ± 0.6 vs. 4.8 ± 0.3 ; $P < 0.01$ for group \times plasma glucose interaction) and of food-related words (6.2 ± 0.6 vs. 4.9 ± 0.4 ; $P < 0.05$ for group \times plasma glucose interaction) but not for recall of neutral words (5.0 ± 0.7 vs. 3.9 ± 0.5 ; $P = 0.24$ for group \times plasma glucose interaction).

Indicators of the arousal state and neuroendocrine counterregulatory hormones

Table 1 summarizes the results of the symptom and mood questionnaire and the blood pressure, heart rate, and counterregulatory hormone measurements. At baseline, none of the self-rated symptom and mood scores differed between the groups. Although scores of some psychological

parameters changed with time during the clamp, none of them differed between the groups at the different hypoglycemic levels. Heart rate and systolic blood pressure increased and diastolic blood pressure decreased during the hypoglycemic clamp, but no difference was evident between the 2 groups. Counterregulatory hormone response to hypoglycemia was significantly reduced after antecedent hypoglycemia.

Multiple regression analysis

Table 2 summarizes correlation coefficients between changes in performance on cognitive function tests and changes in self-rated symptom and mood scores as well as in counterregulatory hormones during hypoglycemia. Changes in P3 amplitude (at Pz) did not correlate with changes in self-ratings and in counterregulatory hormones. However, the increase in P3 latency (at Pz) during hypoglycemia was significantly related to increased epinephrine release (0.045 ± 0.014 ; $P < 0.001$) and to loss of self-rated concentration (23.413 ± 7.291 ; $P < 0.005$, $R^2 = 0.47$).

The decrease in reaction time correlated with self-rated concentration and fatigue. However, multiple regression analysis confirmed a dependence of reaction time only from fatigue (49.65 ± 13.03 ; $R^2 = 0.34$, $P < 0.001$). The decrease in word recall also correlated with increased fatigue and increased release of cortisol and epinephrine. However, multiple regression analysis confirmed that the changes in cortisol (-0.328 ± 0.112 ; $P < 0.005$) and the group factor (2.681 ± 1.230 ; $P < 0.05$) were independently related to the changes in word recall ($R^2 = 0.44$) (Fig. 3).

CONCLUSIONS — This study assessed the effects of antecedent hypoglycemia on hypoglycemic cognitive dysfunction during

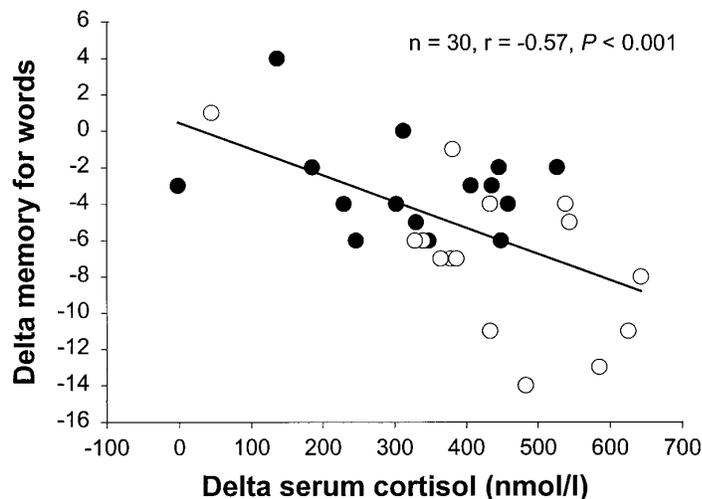


Figure 3—Pearson's correlation between the changes in serum cortisol concentration and the changes in performance of short-term memory recall at the final hypoglycemic plateau. Changes were defined by the difference from the respective baseline value. ●, Prior-hypo group; ○, control group.

subsequent hypoglycemia (i.e., the question of whether a cognitive adaptation to repeated hypoglycemia is involved). Cognitive dysfunction during hypoglycemia was found to be attenuated in men experiencing their second hypoglycemic episode within 24 h compared with the subjects who were not subjected to a mild antecedent hypoglycemia.

It has recently been suggested that psychological factors (e.g., anxiety or fatigue) may confound cognitive performance during hypoglycemic clamp experiments (22). Therefore, in the present study, we monitored self-rated symptom and mood scores as well as physiological indicators of arousal. None of these measures significantly differed between the groups with and without antecedent hypoglycemia. Nevertheless, small differences in fatigue and concentration that may have biased findings cannot be excluded. However, multiple regression analysis did not reveal any evidence that the preserving effects of antecedent hypoglycemia on P3 amplitude and word recall (i.e., the measures most sensitive to antecedent hypoglycemic effects) were dependent on subjective fatigue or concentration. Therefore, an essential contribution of these factors to the effects of antecedent hypoglycemia on cognitive function tests is very unlikely. Also, differences in experience with the experimental procedure by themselves probably cannot explain the observed differences in hypoglycemia-associated cognitive dysfunction between both groups

because all of the men studied had participated in a series of comparable experiments before. However, the men in the control group were not exposed to the antecedent clamp procedure on the day before cognitive testing, which could have resulted in an acutely greater familiarity with the laboratory environment for the prior-hypo group.

The finding of relatively preserved cognitive function after antecedent hypoglycemia agrees with previous data (14,15,25,26,36). On the other hand, several other studies (6,7,23) failed to reveal similar effects of recurrent hypoglycemia. This inconsistency may be explained by differences in the study design. First, methods to assess cognitive dysfunction and related aspects of cognitive function are known to differ in sensitivity regarding the effects of hypoglycemia (22,37–40). Tests used in some foregoing trials may have been not optimal to reveal protective effects of antecedent hypoglycemia. Also, some foregoing studies were based on a fairly small or heterogeneous subject sample (6,7,14,23). Because the size of cognitive changes after antecedent hypoglycemia is only moderate, the statistical power of these studies may have been insufficient. Finally, for all measurements, cognitive dysfunction did not develop in the present study until a hypoglycemic level of 2.6 mmol/l was reached (i.e., after ~5 h of the clamp). This result agrees with previous data (27–30). Only at this plateau, when hypoglycemic disturbances of cognitive function were most pro-

nounced, could the influence of antecedent hypoglycemia be discriminated. With this background, some foregoing experimental hypoglycemic conditions may have been just too mild to detect acute effects (7).

A potential mechanism underlying cerebral adaptation to hypoglycemia could be an increase in glucose extracted during hypoglycemia (41,42). An improved glucose uptake into the brain has been demonstrated after prolonged hypoglycemia in rats (43) and humans (11). Moreover, in rats (44,45), expression of glucose transporter (GLUT1 and GLUT3) molecules was increased after prolonged hypoglycemia. Improved central glucose uptake during hypoglycemia may prevent neuroglycopenia, thereby reducing the effect of hypoglycemia on cognitive function aside from a parallel weakening of neuroendocrine counterregulation and autonomic and neuroglycopenic symptoms.

In addition, weakened neuroendocrine counterregulation after antecedent hypoglycemia may contribute to the attenuated cognitive impairment during subsequent hypoglycemia. Many of the hormones involved in hypoglycemia counterregulation exert neurocognitive influences. For example, in healthy men, short-term elevation of cortisol levels impaired declarative memory performance (46) as well as event-related potential signs of sensory discrimination (47). Therefore, lower hypoglycemic cortisol release after antecedent hypoglycemia may have added to the preserving effects of antecedent hypoglycemia on short-term memory performance in the present study. This view is also supported by the strong association between the response of cortisol and performance on the word recall task to hypoglycemia (Fig. 3), although regression analysis cannot be used to prove a causal relationship.

It has been well established that recurrent severe hypoglycemic episodes adversely affect several aspects of cognitive function over the long term (17–20). With this background, the significance of a cognitive adaptation to hypoglycemia, as indicated herein, in the progress of central nervous system sequelae of diabetes remains to be defined. A cerebral adaptation to hypoglycemia has been regarded as maladaptive because of the weakened glucose counterregulation and resulting hypoglycemic unawareness, which increases the risk of severe hypoglycemia. On the other hand, adaptation to hypoglycemia in terms of increased glucose extraction may also be

beneficial because it not only reduces cognitive dysfunction but also may protect against structural brain damage during severe or recurrent hypoglycemia.

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References

- Cryer PE, Fisher JN, Shamon H: Hypoglycemia. *Diabetes Care* 17:734–755, 1994
- Diabetes Control and Complications Trial Research Group: Adverse events and their association with treatment regimens in the Diabetes Control and Complications Trial. *Diabetes Care* 18:1415–1427, 1995
- Berger M, Muhlhauser I: Diabetes care and patient-oriented outcomes. *JAMA* 281:1676–1678, 1999
- Gerich JE, Mokan M, Veneman T, Korytkowski M, Mitrakou A: Hypoglycemia unawareness. *Endocr Rev* 12:356–371, 1991
- Davis MR, Mellman M, Shamon H: Further defects in counterregulatory responses induced by recurrent hypoglycemia in IDDM. *Diabetes* 41:1335–1340, 1992
- Lingenfeller T, Renn W, Sommerwerck U, Jung MF, Buettner UW, Zaiser-Kaschel H, Kaschel R, Eggstein M, Jakober B: Compromised hormonal counterregulation, symptom awareness, and neurophysiological function after recurrent short-term episodes of insulin-induced hypoglycemia in IDDM patients. *Diabetes* 42:610–618, 1993
- Dagogo-Jack SE, Craft S, Cryer PE: Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus: recent antecedent hypoglycemia reduces autonomic responses to, symptoms of, and defense against subsequent hypoglycemia. *J Clin Invest* 91:819–828, 1993
- Heller SR, Cryer PE: Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. *Diabetes* 40:223–226, 1991
- Davis MR, Shamon H: Counterregulatory adaptation to recurrent hypoglycemia in normal humans. *J Clin Endocrinol Metab* 73:995–1001, 1991
- Davis SN, Shavers C, Mosqueda-Garcia R, Costa F: Effects of differing antecedent hypoglycemia on subsequent counterregulation in normal humans. *Diabetes* 46:1328–1335, 1997
- Boyle PJ, Nagy RJ, O'Connor AM, Kempers SF, Yeo RA, Qualls C: Adaptation in brain glucose uptake following recurrent hypoglycemia. *Proc Natl Acad Sci USA* 91:9352–9356, 1994
- George E, Harris N, Bedford C, Macdonald IA, Hardisty CA, Heller SR: Prolonged but partial impairment of the hypoglycaemic physiological response following short-term hypoglycaemia in normal subjects. *Diabetologia* 38:1183–1190, 1995
- Widom B, Simonson DC: Intermittent hypoglycemia impairs glucose counterregulation. *Diabetes* 41:1597–1602, 1992
- Hvidberg A, Fanelli CG, Hershey T, Terkamp C, Craft S, Cryer PE: Impact of recent antecedent hypoglycemia on hypoglycemic cognitive dysfunction in nondiabetic humans. *Diabetes* 46:1031–1036, 1996
- Veneman T, Mitrakou A, Mokan M, Cryer PE, Gerich J: Induction of hypoglycemia unawareness by asymptomatic nocturnal hypoglycemia. *Diabetes* 42:1233–1237, 1993
- Fruehwald-Schultes B, Kern W, Deininger E, Wellhoener P, Kerner W, Born J, Fehm HL, Peters A: Protective effect of insulin against hypoglycemia-associated counterregulatory failure. *J Clin Endocrinol Metab* 84:1551–1557, 1999
- Hershey T, Bhargava N, Sadler M, White NH, Craft S: Conventional versus intensive diabetes therapy in children with type 1 diabetes: effects on memory and motor speed. *Diabetes Care* 22:1318–1324, 1999
- Gonder-Frederick L, Cox D, Kovatchev B, Schlundt D, Clarke W: A biopsychobehavioral model of risk of severe hypoglycemia. *Diabetes Care* 20:661–669, 1997
- Deary IJ, Crawford JR, Hepburn DA, Langan SJ, Blackmore LM, Frier BM: Severe hypoglycemia and intelligence in adult patients with insulin-treated diabetes. *Diabetes* 42:341–344, 1993
- Rovet J, Alvarez M: Attentional functioning in children and adolescents with IDDM. *Diabetes Care* 20:803–810, 1997
- Fanelli CG, Pampanelli S, Porcellati F, Bolli GB: Shift of glycaemic thresholds for cognitive function in hypoglycaemia unawareness in humans. *Diabetologia* 41:720–723, 1998
- Amiel SA: Cognitive function testing in studies of acute hypoglycaemia: rights and wrongs? *Diabetologia* 41:713–719, 1998
- Robinson AM, Parkin HM, Macdonald IA, Tattersall RB: Antecedent hypoglycaemia in non-diabetic subjects reduces the adrenaline response for 6 days but does not affect the catecholamine response to other stimuli. *Clin Sci (Colch)* 89:359–366, 1995
- Ovalle F, Fanelli CG, Paramore DS, Hershey T, Craft S, Cryer PE: Brief twice-weekly episodes of hypoglycemia reduce detection of clinical hypoglycemia in type 1 diabetes mellitus. *Diabetes* 47:1472–1479, 1998
- Fanelli CG, Paramore DS, Hershey T, Terkamp C, Ovalle F, Craft S, Cryer PE: Impact of nocturnal hypoglycemia on hypoglycemic cognitive dysfunction in type 1 diabetes. *Diabetes* 47:1920–1927, 1998
- Mellman MJ, Davis MR, Brisman M, Shamon H: Effect of antecedent hypoglycemia on cognitive function and on glycemic thresholds for counterregulatory hormone secretion in healthy humans. *Diabetes Care* 17:183–188, 1994
- Widom B, Simonson DC: Glycemic control and neuropsychologic function during hypoglycemia in patients with insulin-dependent diabetes mellitus. *Ann Intern Med* 112:904–912, 1990
- Mitragou A, Ryan C, Veneman T, Mokan M, Janssen T, Kiss I, Durrant J, Cryer P, Gerich J: Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. *Am J Physiol* 260:E67–E74, 1991
- Blackman JD, Towle VL, Sturis J, Lewis GF, Spire JP, Polonsky KS: Hypoglycemic thresholds for cognitive dysfunction in IDDM. *Diabetes* 41:392–399, 1992
- Fanelli C, Pampanelli S, Epifano L, Rabbotti AM, Ciofetta M, Modarelli F, Di Vincenzo A, Annibale B, Lepore M, Lalli C, Del Sindaco P, Brunetti P, Bolli GB: Relative roles of insulin and hypoglycaemia on induction of neuroendocrine responses to, symptoms of, and deterioration of cognitive function in hypoglycaemia in male and female humans. *Diabetologia* 37:797–807, 1994
- Donchin E: Surprise! Surprise? *Psychophysiology* 18:493–513, 1981
- Verleger R: Toward an integration of P3 research with cognitive neuroscience. *Behav Brain Sci* 21:150–152, 1998
- Donchin E, Coles MGH: Context updating and the P300. *Behav Brain Sci* 21:152, 1998
- Kern W, Schlosser C, Kerner W, Pietrowsky R, Born J, Fehm HL: Evidence for effects of insulin on sensory processing in humans. *Diabetes* 43:351–356, 1994
- Peters A, Rohloff F, Kerner W: Preserved counterregulatory hormone release and symptoms after short term hypoglycemic episodes in normal men. *J Clin Endocrinol Metab* 80:2894–2898, 1995
- Fanelli C, Pampanelli S, Ciofetta M, Bolli G: Effect of duration of recent antecedent hypoglycemia on responses to subsequent hypoglycemia in humans (Abstract). *Diabetologia* 40 (Suppl. 1):A235, 1997
- Ryan CM, Atchison J, Puczynski S, Puczynski M, Arslanian S, Becker D: Mild hypoglycemia associated with deterioration of mental efficiency in children with insulin-dependent diabetes mellitus. *J Pediatr* 117:32–38, 1990
- Holmes CS, Koepke KM, Thompson RG: Simple versus complex performance impairments at three blood glucose levels. *Psychoneuroendocrinology* 11:353–357, 1986
- Holmes CS, Koepke KM, Thompson RG, Gyves PW, Weydert JA: Verbal fluency and naming performance in type I diabetes at different blood glucose concentrations. *Diabetes Care* 7:454–459, 1984

40. Holmes CS, Hayford JT, Gonzalez JL, Weydert JA: A survey of cognitive functioning at different glucose levels in diabetic persons. *Diabetes Care* 6:180-185, 1983
41. McCall AL: IDDM, counterregulation, and the brain. *Diabetes Care* 20:1228-1230, 1997
42. Boyle PJ, Kempers SF, O'Connor AM, Nagy RJ: Brain glucose uptake and unawareness of hypoglycemia in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 333:1726-1731, 1995
43. McCall AL, Fixman LB, Fleming N, Tornheim K, Chick W, Ruderman NB: Chronic hypoglycemia increases brain glucose transport. *Am J Physiol* 251:E442-E447, 1986
44. Kumagai AK, Kang YS, Boado RJ, Pardridge WM: Upregulation of blood-brain barrier GLUT1 glucose transporter protein and mRNA in experimental chronic hypoglycemia. *Diabetes* 44:1399-1404, 1995
45. Uehara Y, Nipper V, McCall AL: Chronic insulin hypoglycemia induces GLUT-3 protein in rat brain neurons. *Am J Physiol* 272: E716-E719, 1997
46. Kirschbaum C, Wolf OT, May M, Wippich W, Hellhammer DH: Stress- and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. *Life Sci* 58:1475-1483, 1996
47. Born J, Kern W, Fehm-Wolfsdorf G, Fehm HL: Cortisol effects on attentional processes in man as indicated by event-related potentials. *Psychophysiology* 24:286-292, 1987