Neurophysiological Impairments in IDDM Patients During Euglycemia and Hypoglycemia

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OBJECTIVE — To test the hypothesis that latencies of evoked potentials in IDDM patients are delayed compared with healthy control subjects during euglycemia, and that insulin-induced hypoglycemia causes further latency delays of evoked potentials to occur.

RESEARCH DESIGN AND METHODS — We recruited 23 IDDM patients (27.9 ± 1.6 yr of age, HbA_{1c} 6.7 ± 0.3%, without sensory or autonomic neuropathy) and 26 unequivocally healthy subjects who were carefully matched for sex, age, and body mass index to serve as the control group (18 men and 8 women, 28.4 ± 1.6 yr of age, 22.6 ± 0.7 kg/m^2), for a controlled, prospective study. Sequential euglycemic-hypoglycemic clamps were performed with stable glycemic plateaus of 5.6, 3.3, 2.2, and 1.7 mM, at which the patients' and healthy control subjects' neurophysiological functions were evaluated. The methodological armamentarium included the measurement of brainstem auditory, middle-latency auditory, and somatosensory evoked potentials that assessed conduction velocity in corresponding neural structures and information processing in the midbrain and auditory cortex.

RESULTS — Multiple analysis of variance revealed a significant overall difference of brainstem auditory evoked potential latencies during euglycemia between the study group and healthy control group ($F = 3.41$, $P < 0.03$), which was mainly attributable to latency delays of wave III ($F = 6.60$, $P < 0.02$), V ($F = 9.19$, $P < 0.01$), and interpeak latency I-V ($F = 2.82$, $P < 0.07$). Repeated analysis of variance measures detected a significant latency delay of the major wave P_a of the middle-latency auditory evoked potentials during hypoglycemia ($F = 4.4$, $P < 0.02$), which rapidly returned to normal after reinstitution of euglycemia.

CONCLUSIONS — In IDDM patients, chronic, structural CNS changes already appear at the brainstem level during euglycemia. Functional, reversible CNS changes, however, seem to emerge during acute deviation from glucose homeostasis in more rostral brain regions.

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IDDM, insulin-dependent diabetes mellitus; BAEP, brainstem auditory evoked potential; SSEP, somatosensory evoked potential; MLAEP, middle-latency auditory evoked potential; BMI, body mass index; CV, coefficient of variation; MANOVA, multivariate analysis of variance; ANOVA, analysis of variance; ANCOVA, analysis of covariance; MRI, magnetic resonance imaging.

Glucose is the essential metabolic fuel for the brain (1). Thus, acute deteriorations of glucose homeostasis are likely to cause an instant, but temporary, impairment of cerebral functions (1–3). Recurrent hypoglycemic episodes over days were also shown to reversibly impair cerebral function, as assessed from neurophysiological measurements (4). Chronic hyperglycemia prevails in IDDM; thus, long-term changes caused by glucotoxicity are likely to occur in brain morphology (5). DeJong (6) coined the term "diabetic encephalopathy" for these severe clinical and histopathological CNS abnormalities in long-standing diabetes mellitus. In fact, chronic hyperglycemia per se induces vascular and/or metabolic disturbances and eventually brain disfunction (7,8). The putative mechanisms involved in brain disfunction, may be explained on the basis of the hypotheses of acidotoxic and excitotoxic brain damage by chronic hyperglycemia (8).

Neurophysiological measurements have been applied in the practice of neurology for more than three decades (9,10). Recording of electrical events occurring along the auditory and somatosensory pathways, evoked by repeated presentation of adequate stimuli, are thought to be an objective and noninvasive diagnostic tool in the detection of even subclinical CNS impairments (9,10). Early BAEPs and SSEPs primarily represent the conduction velocity in the corresponding neural structure (auditory or somatosensory pathways) (11,12). However, late BAEPs and MLAEPs are thought to preferentially reflect information processing in the midbrain and the auditory cortex (13–15).

BAEPs and SSEPs have recently been applied on the evaluation of neurophysiological function in IDDM patients during euglycemia (16–23). Mainly because of methodological flaws (patient selection, recording conditions, and interpretation of data), the results were surprisingly contradictory. Furthermore,

only one study focused on the influence of acute changes in glucose homeostasis in diabetic subjects suffering similarly from the methodological limitations mentioned previously (24). Thus, we decided to first evaluate cerebral function and peripheral transmission as assessed from evoked potentials during euglycemia. This research was conducted in carefully selected IDDM patients under well-defined recording conditions according to widely accepted standards. Secondly, to assess the impact of hypoglycemia per se on the neurophysiological capacity, we applied the glucose clamp technique to achieve different but stable hypoglycemic plateaus.

By doing so, we tested the hypothesis that latencies of evoked potentials (BAEP, MLAEP, and SSEP) in IDDM patients are significantly delayed compared with healthy control subjects during euglycemia. The second hypothesis comprises the assumption that insulin-induced hypoglycemia in IDDM patients causes further latency delays of evoked potentials to occur.

RESEARCH DESIGN AND METHODS

— We recruited 23 young IDDM patients (17 men and 6 women, 27.9 ± 1.6 yr of age [mean ± SE], diabetes manifestation of 8.5 ± 1.1 yr [range 2–17 yr, 9 patients developed IDDM later than adolescence, >18 yr], HbA_{1c} 6.7 ± 0.3% [normal range 4.1–6.3%], and BMI 23.9 ± 0.7 kg/m^2) for a controlled, prospective study. No evidence was found of sensory or autonomic neuropathy, which was assessed from the normal cardiovascular reflexes such as 30/15 ratio, R-R variation on breathing, Valsalva maneuver, and postural hypotension (25). No other diseases were present, and medication included insulin exclusively.

All of the IDDM patients participated in the evaluation of BAEPs. In the evaluation of MLAEPs, 18 patients participated (14 men and 4 women, 26.7 ± 1.0 yr of age, diabetes manifestation of 8.2 ± 1.1 yr [range 2–16 yr] [7 patients >18 yr], HbA_{1c} 6.8 ± 0.3%, and BMI 22.9 ± 0.9 kg/m^2). In the evaluation of SSEPs, 10 patients participated (6 men and 4 women, 29.9 ± 1.0 yr of age, diabetes manifestation of 8.6 ± 0.6 yr [range 3–12 yr] [6 patients >18 yr], HbA_{1c} 6.3 ± 0.3%, and BMI 23.9 ± 0.2 kg/m^2). The control group comprised 26 unequivocally healthy subjects who were carefully matched for sex, age, and BMI (18 men and 8 women, 28.4 ± 1.6 yr of age, BMI 22.6 ± 0.7 kg/m^2). Approval was obtained from the local ethical committee according to the Declaration of Helsinki, and the patients gave informed consent.

The patients were kept fasting overnight, and the usual isophane insulin evening dose was withdrawn. After cannulating antecubital and dorsal hand veins with indwelling catheters, the blood glucose concentration (arterialized by heated chamber) was clamped at ~5.6 mM by means of a glucose controlled insulin infusion system (Biostator, Life Science Instruments, Miles, Elkhart, IN) (26). Blood glucose concentration was measured in duplicate by a glucose dehydrogenase method (Eppendorf ACP 5040, Hamburg, Germany) after deproteinization of whole blood with uranylacetate. Blood glucose concentrations determined in deproteinized whole blood are usually 90% of that determined in deproteinized plasma. At 0630 the next morning, the blood glucose concentration was lowered stepwise to 3.3, 2.2, and 1.7 mM, respectively (Fig. 1), by external infusion of regular insulin at a constant rate of 2 mU · kg^{-1} · min^{-1} as described previously (27). At the preselected plateaus, blood glucose was held constant for 30 min (3.3/2.2 mM) or 20 min (1.7 mM), respectively. The neurophysiological measurements were taken 5 min after reaching each stable plateau and lasted 15–20 min. Euglycemia was rapidely re-established after the 1.7 mM plateau (Fig. 1).

Patients were informed that blood glucose would drop to hypoglycemic levels, but were kept ignorant about

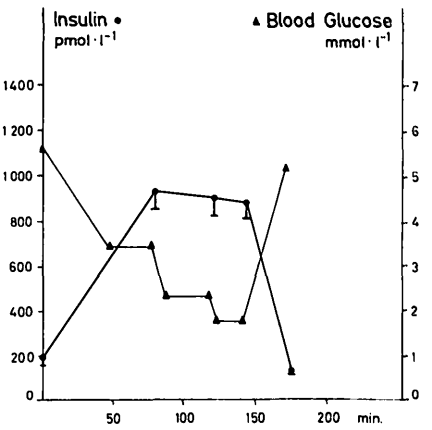

Figure 1—*Mean blood glucose and insulin concentrations during the hypoglycemic clamps (see* METHODS).

the actual glucose levels throughout the study. By applying these methods, glucose homeostasis (euglycemia) could be kept constant overnight in all patients. Furthermore, these techniques allowed us to achieve similar hypoglycemic plateaus in all patients. Glucose requirements for the maintenance of stable blood glucose concentrations at the preselected plateaus were not significantly different (294 ± 20 mg/min at 3.3 mM; 277 ± 23 mg/min at 2.2 mM; and 309 mg/min at 1.7 mM). By selecting appropriate algorithms in the glucose clamp program, the CVs of blood glucose concentrations at these plateaus could be limited to between 0.8 (3.3 mM) and 2.9% (1.7 mM). Constant external insulin infusion resulted in equal blood insulin concentrations throughout the hypoglycemic clamps, as depicted in Fig. 1 (3.3, 2.2, and 1.7 mM: 926.1 ± 71.1, 898.4 ± 76.2, and 883.7 ± 70.2 pM, respectively). Free insulin was measured with the Enzymun-Test Insulin, ELISA from Boehringer Diagnostica (Mannheim, Germany), from serum without prior protein precipitation (one-step sandwich-assay), CV 2.1–9.1%.

Patients were seated in a semirecumbent position in a quiet, warm room; the position of the head being adjusted

for maximum relaxation of the neck muscles. The room temperature was strictly controlled by air-conditioning and kept at 24°C. BAEPs (28) were recorded on-line according to widely accepted standards with platinum needle electrodes (Disa 25 C 04) at the ipsilateral mastoids referenced against C_z (international 10–20 system for EEG registration) that were amplified and averaged with a Medelec (MS 92a, Medelec Limited, Surrey, England) using a bandpass of 200-2000 Hz (Butterworth filter, slope 12db/octave). The 70-dB sensation level and rarefaction clicks (pulse duration 100 μs) with a repetition rate of 10 Hz were delivered monoaurally by electromagnetically shielded earphones (DT 48 A.0, Beyerdynamic, Heilbronn, Germany) after determination of the individual hearing threshold for our clicks (to minimize differences in hearing sensitivity). Hearing threshold measurements were not performed. Analysis time was 10 ms in 2048 single measurements.

In 18 patients, MLAEPs (28) were recorded under similar conditions, apart from a different bandpass of 20–2000 Hz. SSEPs (28) were recorded in 10 patients following stimulation of the median nerve at the wrist with 0.2-ms square-wave pulses, delivered at 4 mA above the motor threshold. Platinum needles were inserted subcutaneously over the contralateral somatosensory representation either at C_3' or C_4' against a F_z reference. The potentials were amplified and averaged with a bandpass of 20–2000 Hz and a resolution of 256 data points (analysis time 50 ms).

The peaks of interest (latencies [ms], interpeak latencies [ms], and peak-to-peak amplitudes [μV]) (28) were analyzed off-line by a neurologist who was unaware of the glycemic plateau at which the evoked potentials were registered (Figs. 2 and 3). The major waves were classified according to international nomenclature (SSEP: N20; BAEP: I, III, and V; MLAEP: N_0, P_0, N_a, and P_a). They had been applied in previous studies from our group (11,12) and were selected because they specifically allow evaluation of neurophysiological function (14).

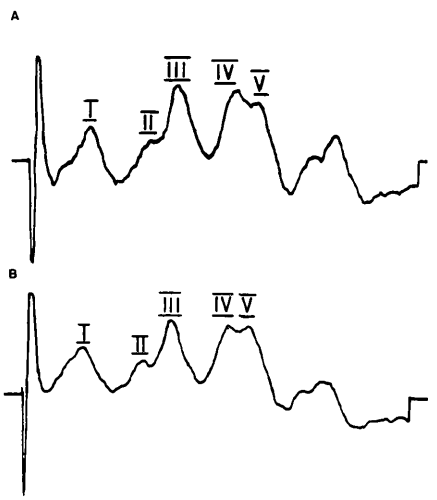

Figure 2—*Traces of BAEPs, including wave I, III, and V in an individual patient (ipsilateral mastoid recording referenced against C_z) at 5.6 (A) and 1.7 mM (B). Latency of wave V is not different during euglycemia and hypoglycemia (5.9 ms at both plateaus).*

Statistical analysis

Data are expressed as means ± SD. Examination of the correlation matrix revealed a high correlation of evoked potential measures, thereby ruling out treatment as independent variables. Thus, MANOVA was applied to compare neurophysiological measurements of diabetic patients with those of normal control subjects. A separate comparison within each group of evoked potentials necessitated α-adjustment for related measures. Subsequent univariate ANOVA was applied to determine which variables contribute to the overall differences. Effects of blood glucose concentration on neurophysiological measurements were assessed by repeated ANOVA measures. Because two-way repeated ANOVA measures are not available, the related measures of representative evoked potentials also necessitated Bonferroni-type correction of α-level.

RESULTS — Reliable BAEP, MLAEP, and SSEP measurements were available from every IDDM patient and healthy control subject. Therefore, inter- and intraindividual changes of evoked potentials before and consecutive to a decrease of blood glucose concentration could be determined. MANOVA within each group of evoked potentials (SSEP, BAEP, and MLAEP) revealed a significant overall difference of the BAEP latencies (I, III, and V) during euglycemia between the study group of IDDM patients and a group of matched control subjects (Table 1, $P < 0.03$). Univariate testing of each BAEP variable allocated this difference mainly to delayed latencies of wave III (3.84 ± 0.21 vs. 3.71 ± 0.17 ms; $F = 6.60$, $P < 0.02$) and V (5.78 ± 0.25 vs. 5.60 ± 0.16 ms; $F = 9.19$, $P < 0.01$). Latencies of wave I did not differ between either group (1.69 ± 0.13 vs. 1.63 ± 0.15 ms; $F = 2.68$, NS). By inference, the interpeak latencies V-I seem to be different, but this difference just failed to reach statistical significance (4.09 ± 0.29 vs. 3.97 ± 0.16 ms; $F = 2.82$, $P < 0.07$). The same was true

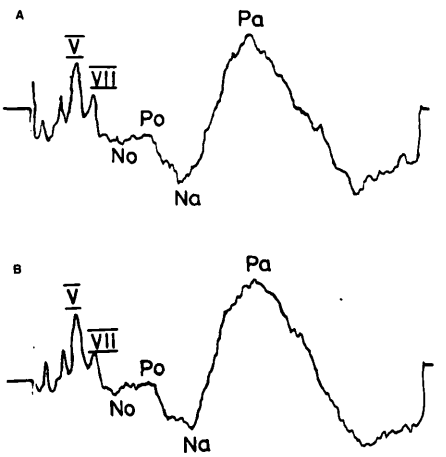

Figure 3—*Traces of MLAEPs, including wave N_0, P_0, N_a, and P_a in an individual patient (ipsilateral mastoid recording reference against C_z) at 5.6 mM (A) and 1.7 mM (B). Latency of wave P_a is prolonged during hypoglycemia compared with euglycemia (B vs. A: 29.5 vs. 28.5 ms).*

Table 1—*Latencies (ms) of evoked potentials in IDDM patients and normal control subjects during euglycemia*

	IDDM patients	Normal control subjects	F value	Significance of F
SSEP				
n	10	26		
N20	19.1 ± 0.8	19.0 ± 0.9	0.09	NS
BAEP				
n	23	26		
I	1.69 ± 0.13	1.63 ± 0.15	3.41	$P < 0.03$
III	3.84 ± 0.21	3.71 ± 0.17		
V	5.78 ± 0.25	5.60 ± 0.16		
MLAEP				
n	18	26		
N_0	9.44 ± 0.66	9.51 ± 0.99	2.25	NS
P_0	12.64 ± 1.37	12.38 ± 0.77		
N_a	17.96 ± 2.55	17.02 ± 1.35		
P_a	29.57 ± 3.48	30.03 ± 2.38		

Data are means ± SD. MANOVA for the effect of diabetes on neurophysiological measurements within each group of evoked potentials (brackets join the group of measurements to which MANOVA is applied: I, III, V for BAEP; N_0, P_0, N_a, P_a for MLAEP).

for the difference of interpeak-latencies V-III (1.94 ± 0.16 vs. 1.89 ± 0.13, $F = 1.63$, NS). BAEP measurements from 23 IDDM patients were outside the normal range (defined as values >2 SD from mean) as follows: latency of wave I in 2 (8.71%) patients, of wave III in 6 (26.1%) patients, of wave V in 7 (30.4%) patients, and interpeak-latency V-I in 7 (30.4%) patients. This subgroup of patients with neurophysiologically abnormal values did not differ from the remaining subjects with regard to demographic or clinical characteristics (25.1 ± 0.9 yr of age, with diabetes manifestation of 9.0 ± 2.0 yr [2 patients >18 yr], HbA_{1c} 6.9 ± 0.5%, and BMI 23.6 ± 0.7 kg/m^2). Furthermore, a careful medical history did not reveal a higher prevalence of hypoglycemia in these patients. No differences between diabetic patients and normal control subjects were detectable by SSEP measurements in N20 latencies (Table 1) and in N20 amplitudes (2.1 ± 0.7 vs. 2.3 ± 1.1 ms; $F = 1.74$, NS).

MANOVA of MLAEP measurements did not show a significant overall difference of latencies (N_0, P_0, N_a, and P_a) between groups (Table 1, $F = 2.25$, NS). In fact, univariate testing confirmed these findings for all MLAEP variables (N_0: 9.44 ± 0.66 vs. 9.37 ± 0.75 ms, $F = 0.13$, NS; P_0: 12.67 ± 1.38 vs. 12.45 ± 0.68 ms, $F = 0.49$, NS; N_a: 17.96 ± 2.55 vs. 17.15 ± 1.12, $F = 2.05$, NS; P_a: 29.19 ± 3.51 vs. 30.18 ± 1.95 ms, $F = 1.44$, NS). Latencies exceeded the normal range (>2SD) in only 2 patients for wave P_0, 2 patients for wave N_a, and 1 patient in P_a. These patients also had prolonged BAEPs. Because three groups of evoked potentials were examined, α-adjustment for related measures (Bonferroni) was performed that resulted in an α-level of <0.018. Thus, the original differences in BAEP latencies between diabetic patients and healthy control subjects would just fail to reach statistical significance. Note, however, that Bonferroni-type correction usually yields rather conservative statistical estimations.

Repeated ANOVA measures of representative latencies of evoked potentials (V, N20, and P_a) were unable to detect any effect of the actual metabolic status, that is to say, of acute hypoglycemia on BAEP latencies (Table 2, $F = 1.45$, NS). Earlier BAEP latencies were as follows: wave I (1.69 ± 0.13, 1.72 ± 0.17, 1.72 ± 0.19, 1.73 ± 0.18, and 1.72 ± 0.14 ms); wave III (3.84 ± 0.21, 3.88 ± 0.17, 3.86 ± 0.16, 3.88 ± 0.18, and 3.85 ± 0.15 ms); and interpeak-latency V-I (4.09 ± 0.29, 4.05 ± 0.25, 4.05 ± 0.29, 4.07 ± 0.30, and 4.06 ± 0.28). For SSEP measures, a similar situation emerged revealing extremly constant N20 latencies (Table 2) and amplitudes (2.1 ± 0.7, 2.4 ± 1.4, 1.9 ± 1.1, 2.0 ± 1.3, and 2.3 ± 1.6 μV) across blood glucose concentration (Table 2, $F = 0.69$, NS). In contrast, repeated measures of ANOVA for late

Table 2—*Effects of hypoglycemia on representative latencies (ms) of evoked potentials in IDDM patients*

	5.6 mM	3.3 mM	2.2 mM	1.7 mM	Recovery	F value	Significance of F
N20	19.10 ± 0.80	19.10 ± 0.70	19.30 ± 0.80	19.30 ± 0.70	19.20 ± 0.60	0.69	NS
V	5.78 ± 0.25	5.77 ± 0.24	5.77 ± 0.22	5.80 ± 0.24	5.77 ± 0.28	1.45	NS
P_a	29.57 ± 3.48	30.22 ± 3.62	30.10 ± 2.90	31.38 ± 3.76	29.80 ± 3.26	4.40	$P < 0.02$

Data are means ± SD. Repeated measures ANOVA for the effect of hypoglycemia on neurophysiological measurements in representative evoked potentials.

MLAEPs (P_a) disclosed a significant, reversible effect of hypoglycemia on neurophysiological measures (Table 2, $F = 4.40$, $P < 0.02$). This effect persisted even after α-adjustment for three related measures (V, N20, and P_a), The remaining MLAEP latencies were as follows: N_0 (9.44 ± 0.66, 9.28 ± 0.70, 9.30 ± 0.85, 9.31 ± 0.87, and 9.17 ± 0.74); P_0 (12.64 ± 1.37, 12.72 ± 0.83, 13.23 ± 0.73, 13.05 ± 1.11, and 12.49 ± 1.14); and N_a (17.96 ± 2.55, 17.55 ± 1.56, 17.84 ± 1.64, 18.13 ± 1.80, and 17.41 ± 2.34). ANCOVA with the euglycemic evoked potential measures as covariates failed to reveal any differences of the hypoglycemia effect in both the BAEPs and MLAEPs.

CONCLUSIONS — These data suggest that, indeed, neurophysiological deteriorations exist in IDDM patients, throughout euglycemic homeostasis, as well as progressive hypoglycemia. This was assessed by means of an array of evoked potentials. Impairments of short-latency evoked potentials during euglycemia indicated chronic, structural CNS changes, whereas impaired middle-latency evoked potentials during hypoglycemia pointed towards acute, functional CNS deviations in this metabolic situation.

Similar intra- and interindividual glucose homeostasis (euglycemic or hypoglycemic plateaus) throughout our entire study could be achieved by appropriate application of the glucose clamp technique. Failure to do so, significantly confounded a correct evaluation of neurophysiological function during different metabolic conditions and may have contributed to the inconsistent observations in preceding studies (16–23).

We found impaired evoked potentials (i.e., latency delays) along the afferent auditory pathway (BAEP), particularly regarding the latencies of wave III and V, and the interpeak latencies of wave V-I thought to represent central transmission time (11,12,14). This included the eighth nerve and brainstem in a homogenous group of young IDDM patients with a moderate duration of the disease. In the absence of hearing threshold measurements, and in view of impaired wave I latencies in the occasional patient, which indicated an end-organ site of lesion, we rather relied on the BAEP components and the interpeak latency V-I (14). In fact, it is commonly thought that delayed eighth nerve and brainstem responses may emerge already a few years after clinical diagnosis and long before appearance of overt peripheral or autonomic neuropathy (16,17,21,22). Not only were later BAEP latencies often prolonged in our IDDM patients, but up to one third fall outside 2SD from the mean of the normal control subjects. Note that the neurophysiologically abnormal patients did not differ from the remaining IDDM subjects with regard to demographics, metabolic control, or prevalence of hypoglycemia. Thus, these features cannot be relied on in the prediction of neurophysiological impairments during early IDDM. The percentage of abnormal BAEP measures agrees with previous findings (17,19,29), whereas a higher percentage has been reported in patients with classical diabetic neuropathy (20).

Although the existence of structural changes in the brain can be deduced from our observations, it is not clear from this study, if diabetic micro- or macroangiopathy or primary diabetic abnormalities of brain tissue constitute the pathogenic mechanism for the disturbed CNS function (8). The presence of small, multiple, and lacunar lesions in areas supplied by paramedian arteries (brainstem area, basal ganglia, pontine basis, and thalamus) on MRI in a subset of patients with BAEP abnormalities (30) points to the former assumption. Note, however, that a few patients had pathological BAEPs, but without such MRI findings (30).

Because of only a discrete, nonsignificant shift of the mean MLAEP latencies in IDDM patients during stable euglycemia, just 2 patients exceeded mean values by >2SD in comparison with normal control subjects. Indeed, the same observation was made by Martini et al.(29). BAEPs may be more sensitive to the structural, plausibly subtle CNS changes than MLAEPs. MLAEPs involve diverse polysynaptic pathways of higher brain regions including the mesencephalic reticular formation and the thalamo-cortical pathways (13,29,31), which may compensate for deficiencies in lower CNS structures. However, the definite significance of MLAEPs for the assessment of the primary auditory cortex is still matter of controversial debate.

Data on neurophysiological measurements during acute deviation from glucose homeostasis are scarce. Those few primarily include measurements of endogenous, event-related, evoked potentials (visual or auditory P_{300}) to assess the impact of hypoglycemia on CNS function (32–36). Note that they are strikingly susceptible to changes in the patient's alertness and cooperation (9), which per se may explain the contradictory results of the studies having been performed to date. Thus, we further relied on the evaluation of the short- and middle-latency evoked potentials. By doing so, we found no effect of the metabolic status on BAEPs and SSEPs. Short-latency potentials have been shown to be extremly resistant to acute metabolic changes (37,38); and, indeed, both Talroth et al. (36) and Amiel et al. (39) failed to reveal SSEP alterations during insulin-induced hypoglycemia. Tight glycemic control in our patients is unlikely to have masked hypoglycemia effects on neurophysiological measurements because SSEPs were shown not to be influenced by long-term metabolic adjustments (39) and MLAEPs may deteriorate remarkably evenly in this patient group (4).

Recent studies that reported abnormal BAEPs during severe (24,40), or even moderate (34) hypoglycemia should be reviewed with scepticism. First, they often lacked controlled conditions and appropriate statistical analysis (40). Second, in contrast with method-

ological recommendations (28,41), BAEP measurements were often just morphologically evaluated (34). The only study in IDDM patients to date recruited a rather heterogenous group of patients (24). That may be the reason why BAEP changes were not consistent throughout all prior variables and appeared patchily during hypoglycemia (24). Further potentially confounding factors, like temperature-related BAEP changes (14,42), have not been corrected.

In contrast, acute hypoglycemia caused significant latency shifts in the most reliable and stable MLAEP component (P_a) (13) to occur. The transient character and instant reversal of these changes after reinstitution of euglycemia indicates functional, but not structural, CNS alterations. Prolonged nerve conduction time via electrolyte changes along nerve fibers, especially in the region of the nodes of Ranvier (43), is caused by acute metabolic derangements (i.e., uremia, hypoxia, and hypoglycemia). Comparable mechanisms are presumed to exist in corresponding CNS structures (41). These electrophysiological events are represented by the latency shifts in the MLAEPs.

Some preliminary evidence exists for a modulatory effect of insulin effect per se on hypoglycemia counterregulation (44) and cognitive function (45), although studies in animals (46) and humans (47) point to neuroglycopenia as the determinant factor of cerebral glucose metabolism. Thus, we did not intend to evaluate such an effect on neurophysiological function in our study. However, we cannot exclude a modulatory impact of the prevailing insulin concentration on the extent of latency delay in the P_a component.

MLAEPs are currently thought to be generated in more rostral brain regions including the auditory cortex (13,14). Hypoglycemia-induced brain injury selectively appeared in rostrocaudal direction, the superficial layers of the cerebral cortex being the most vulnerable areas (48). Thus far, our results support the view of impaired electrocortical activity during hypoglycemia (36,39,49). Note, however, that neuropsychological testing has not been performed in this study, which would have allowed an even more comprehensive evaluation of the functional level impact of low blood glucose concentration (2,3).

Application of an array of evoked potentials in the evaluation of IDDM patients increases the detection rate of neurophysiological impairments in such patients. In clinical terms, they may prove worthwhile in revealing chronic or acute alterations of cerebral function during different metabolic conditions.

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