Hypoglycemia During Sleep Impairs Consolidation of Declarative Memory in Type 1 Diabetic and Healthy Humans

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OBJECTIVE — Early nocturnal sleep enhances the consolidation of declarative memories acquired during prior wakefulness. Patients with type 1 diabetes frequently experience hypoglycemic episodes during sleep. We investigated whether short-lasting hypoglycemia during early nocturnal sleep affects the sleep-associated consolidation of declarative memories.

RESEARCH DESIGN AND METHODS — Sixteen type 1 diabetic patients and 16 healthy subjects matched for age and BMI were tested. On one condition, a linear fall of plasma glucose to 2.2 mmol/l was induced within 60 min by infusing insulin during early sleep. On the control condition, euglycemia (>3.86 mmol/l) was maintained throughout the night. In the morning, subjects recalled word pairs learned in the preceding evening. To assess mood and attention, a symptom questionnaire, an adjective check list, and the Stroop test were applied. Also, auditory event-related brain potentials were recorded.

RESULTS — After euglycemia, subjects recalled 1.5 ± 0.5 more word pairs than after hypoglycemia ($P < 0.01$), remembering 2.0 ± 0.6 more word pairs than at immediate recall before sleep ($P = 0.002$). Across the hypoglycemic night, no such gain occurred (+0.5 ± 0.6 words; $P = 0.41$). Hypoglycemia during sleep also impaired mood ($P < 0.05$) but did not affect attention. Effects compared well between type 1 diabetic patients and healthy control subjects.

CONCLUSIONS — Our findings indicate specific sensitivity of declarative memory consolidation during sleep to rather short episodes of mild hypoglycemia. This effect may disable memory processing in type 1 diabetic patients prone to nocturnal hypoglycemic episodes and underlines the importance of considering sleep as a critical period in the treatment of these patients.

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Hypoglycemic episodes during sleep constitute a particular problem in patients with type 1 diabetes, with incidence rates of up to 56% of nights (1–4). Such episodes can last 1–12 h (2–6) and, except for disturbed awakening behavior (7,8), frequently appear to be asymptomatic (9,10). However, hypoglycemic episodes during nocturnal sleep have been shown to diminish counterregulatory and symptomatic responses to subsequent hypoglycemia (11,12). Whereas the deteriorating impact on cognitive functions of hypoglycemia in the waking state is well known (13), the influences of nocturnal hypoglycemic episodes on cognitive functions and mood on the following day have been rarely investigated. Two studies (14,15) failed to reveal adverse effects of nocturnal hypoglycemia on cognitive functions assessed in the next morning, whereas mood was impaired (15). However, the neurocognitive tests used in these studies mainly assessed aspects of acute stimulus processing, i.e., functions that at the time of testing may have recovered from effects of nocturnal hypoglycemia. No attempt has been made as yet to assess the immediate impact of hypoglycemia on ongoing stimulus processing during sleep.

Increasing evidence suggests that sleep benefits memory consolidation (16–18). In particular, early nighttime sleep, which is characterized by predominant "deep" slow-wave sleep (SWS) enhances the consolidation of declarative memory (19–21). Hence, nocturnal hypoglycemia, especially when it occurs during early SWS-rich periods of sleep, may impair the ongoing consolidation of declarative memories. To examine this hypothesis, we induced short-term hypoglycemia during early nighttime sleep in 16 type 1 diabetic patients and in 16 healthy subjects. In the morning, subjects performed a classical declarative memory task in which word pairs learned in the preceding evening were recalled. To discriminate effects on sleep-associated consolidation from proactive influences of nocturnal hypoglycemia that might lead to a global impairment of cognitive functions in the morning, subjects also performed the Stroop test and an auditory vigilance task including recording of event-related brain potentials (ERPs). Previous studies have indicated that type 1 diabetic patients show distinctly less pronounced sleep disturbances during nocturnal hypoglycemia than healthy subjects (7). Therefore, we studied healthy control subjects in addition to patients with type 1 diabetes, supposing that the potentially impairing influence on memory consolidation may be less pronounced in type 1 diabetic patients than in healthy subjects.

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Abbreviations: CSII, continuous subcutaneous insulin infusion; ERP, event-related brain potential; ICT, intensive conventional therapy; SWS, slow-wave sleep.

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

RESEARCH DESIGN AND METHODS

— Sixteen type 1 diabetic patients (7 women) and 16 healthy control subjects (8 women) matched for age (mean ± SEM, type 1 diabetic patients 31.3 ± 2.6 years and control subjects 28.4 ± 1.5 years) and BMI (type 1 diabetic patients 24.4 ± 0.8 kg/m^2 and control subjects 23.0 ± 0.6 kg/m^2) participated in the experiments. All subjects had a regular sleep-wake cycle during the 4 weeks before the experiments and were not allowed to take naps during the day before experimental nights. The educational level was comparable between type 1 diabetic patients (eight subjects with a high school diploma and eight subjects with a junior high diploma) and healthy control subjects (nine subjects with a high school diploma and seven subjects with a junior high diploma).

Only type 1 diabetic patients without diabetes complications were admitted. Mean ± SEM diabetes duration was 9.1 ± 1.4 years, and A1C was 7.7 ± 0.3%. Twelve patients were receiving an intensive conventional therapy (ICT) regimen with at least three injections of short-acting insulin and one to two injections of long-acting insulin per day. The remaining four patients were receiving continuous subcutaneous insulin infusion (CSII). The patients receiving ICT used the following types of insulin: long-acting insulin (nine patients, insulin glargine; two patients, insulin isophane; and one patient, prompt insulin zinc suspension [a porcine insulin]) and short-acting insulin (six patients, regular human insulin; four patients, insulin aspart; and two patients, insulin lispro). All four patients receiving CSII therapy used insulin lispro in their pumps. The study was approved by the local ethics committee. All subjects gave written informed consent before participation.

After an adaptation night, each subject was tested on two experimental nights spaced at least 2 weeks apart. During one night, hypoglycemia was induced by intravenously infusing insulin (Insuman rapid; Aventis, Bad Soden, Germany). Three minutes after subjects had entered stage 2 sleep for the first time, insulin infusion was started at a continuous rate of 1.5 mU · kg^{-1} · body weight^{-1} · min^{-1} and was continued for 1 h. Plasma glucose, measured every 5 min (Glucose Analyzer II; Beckman, Palo Alto, CA), was allowed to fall in a linear manner to a nadir of 2.2 mmol/l after 60 min. Levels were controlled by simultaneous infusion of a 20% glucose solution whenever necessary. At the nadir concentration of 2.2 mmol/l, insulin infusion was stopped, and plasma glucose levels were immediately restored to the normal range. During the control night, euglycemia (>3.86 mmol/l) was maintained, and spontaneous hypoglycemia was prevented by glucose infusion when necessary, which occurred in five of the patients' control nights. The order of experimental conditions was balanced according to a within-subject crossover design. Subjects were informed about the nature of the experiment but did not know when hypoglycemia would occur. Data regarding the acute counterregulatory responses to hypoglycemia in both groups have been reported previously (8).

On each experimental night, subjects went to bed, and lights were turned off at 2300 h. They were awoken at 630 h. All neurocognitive tests were performed between 2030 and 2215 h in the evening and between 630 and 730 h in the morning after sleep.

Sleep recordings and assessment of mood and neurocognitive functions

Sleep was recorded polysomnographically, and recordings were scored offline according to the standard criteria by Rechtschaffen and Kales (22). In the semiquantitative symptom questionnaire, subjects rated from 0 (none) to 9 (severe) in a total of 27 symptoms (23). Mood was assessed by a standardized adjective checklist (24). Selective attention was assessed using the Stroop test (25). ERPs were recorded during a standard auditory oddball task, which required the subject to discriminate target pips that were randomly interspersed among frequent standard pips of lower pitch. The subjects were instructed to press a button as quickly as possible whenever they discriminated a target pip. A detailed description of ERP recording and analyses is given elsewhere (26,27).

To test declarative memory, a word pair associate learning task consisting of a list of 40 pairs of nouns was used. During the learning phase, the word pairs of the list were presented on a computer screen one after another, with each pair being displayed for 5 s and an interstimulus interval of 100 ms between pairs. Immediately afterward, a cued recall test was performed, where the first word (cue) of each pair was shown alone and the subject was asked to name the second word (associate) of the respective pair within 60 s. Independent of whether or not the subject's response was correct, feedback was given by displaying the correct associate word for 2 s. For example, for the word pair "flag-camp," subjects were presented the word "flag" and were to name the associate "camp." Feedback presentation of the associate word allowed the subject to further encode the word pair and also ensured that at encoding the number of presentations was the same for each word pair of the list. Cued recall of the list of word pairs was repeated until the subject reached a minimum of 24 correct responses (60%) in one trial. The sequence of cue word presentations was randomized across the repeated trials. The number of word pairs recalled in this final criterion trial indicated learning performance before sleep. For retrieval testing after sleep, the same cued recall procedure was used, except that the feedback presentation of the associate words was omitted. Memory retention was determined by the difference (Δ) between the numbers of recalled word pairs at retrieval testing and at learning before sleep. On each experimental night, different lists of word pairs were used.

Statistical analysis

All values are presented as means ± SEM. Statistical analysis was based on ANOVAs including a repeated-measures factor "hypo" for the effects of hypoglycemia versus euglycemia and a repeated-measures factor "time" to reflect differences between evening versus morning. Differences between type 1 diabetic patients and healthy control subjects were reflected by a "group" factor. Changes in memory retrieval were expressed as Δ values (morning − evening) and subjected to ANOVAs including the repeated measures factors hypo and time. Pairwise comparisons for continuous variables relied on Student's *t* tests and on the McNemar test for categorized variables. Pearson correlational analyses were performed to examine the relationships between mood, nocturnal cortisol levels, A1C, and memory performance. $P < 0.05$ was considered significant. The sample size of $n = 16$ for each group (patients and healthy subjects) was based on power analyses including an effect size of 1.07 (as derived from previous studies on effects of sleep on consolidation of word pair memories [28–30]) and a power of 90% at a level of significance of $P < 0.05$ (31).

RESULTS

— Infusion of insulin in the hypoglycemia condition decreased

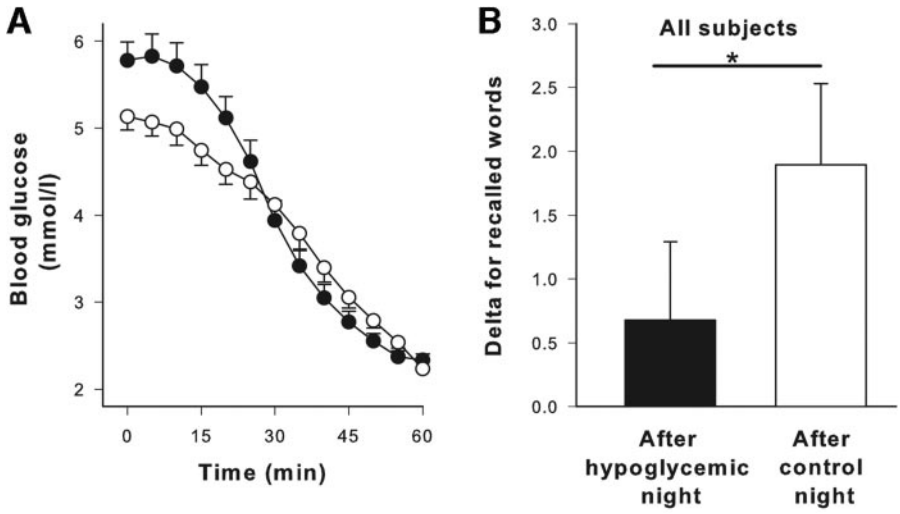

Figure 1— *Plasma glucose concentrations during insulin-induced hypoglycemia* (A) *and declarative memory performance after the hypoglycemic versus euglycemic control night* (B). *Plasma glucose levels (mean ± SEM) were measured in 16 healthy subjects (○) and 16 patients with type 1 diabetes (●) during the first 90 min after they reached sleep stage 2. An insulin infusion started at the first occurrence of sleep stage 2 (0 min) to lower glucose levels to a nadir of 2.2 mmol/l within 60 min. Subsequently, plasma glucose levels were normalized by infusion of a 20% glucose solution. Baseline-adjusted mean numbers of correctly recalled word pairs in the word pair associate learning task (i.e., recall performance at learning in the evening was subtracted from performance in the morning after sleep) in all subjects (type 1 diabetic patients and healthy control subjects).* $^*P < 0.01$.

plasma glucose levels in a linear manner to a nadir level of 2.22 ± 0.01 mmol/l in type 1 diabetic patients and of 2.24 ± 0.02 mmol/l in the healthy subjects ($P = 0.98$) with the temporal dynamics being very similar in both groups (Fig. 1*A*). Because of the insulin infusion, in both type 1 diabetic patients (317 ± 116 vs. 1,110 ± 162 pmol/l; $P = 0.012$) and healthy control subjects (36 ± 8 vs. 1,014 ± 120 pmol/l; $P = 0.001$), serum insulin levels were higher during nocturnal hypoglycemia than during the corresponding time interval of the control night ($P = 0.031$ and $P = 0.41$ for comparisons between type 1 diabetic patients and healthy control subjects; respectively). Analysis of counterregulatory hormonal responses (8) indicated the expected strong increases in plasma concentrations of epinephrine, norepinephrine, and cortisol, which were overall significantly less pronounced in the type 1 diabetic patients than in the healthy control subjects.

Mood

In the morning after nocturnal hypoglycemia, ratings of the semiquantitative symptom questionnaire indicated increased feelings of inner restlessness (2.00 ± 0.49 vs. 0.94 ± 0.49; $P = 0.015$) and fatigue (4.69 ± 0.62 vs. 3.81 ± 0.57; $P = 0.007$) compared with the control night. Subjects also sensed more coldness (1.13 ± 0.45 vs. 0.38 ± 0.26; $P = 0.038$) and felt more sweating (3.00 ± 0.74 vs. 0.88 ± 0.27; $P = 0.021$). Correspondingly, the results of the adjective checklist indicated that subjects felt more tired (0.35 ± 0.48 vs. 0.26 ± 0.04; $P = 0.018$) and depressed (0.06 ± 0.03 vs. 0.04 ± 0.03; $P = 0.036$) after the hypoglycemic night. None of these self-reported alterations depended on whether subjects were diabetic patients ($P > 0.33$ for all comparisons).

Declarative memory and neurocognitive functions

Table 1 summarizes the results of the neurocognitive tests. Patients with type 1 diabetes and healthy subjects did not differ in any of the neurocognitive functions including the word pair associate learning task ($P = 0.76$). However, the learning task revealed distinct differences between the hypoglycemic and euglycemic conditions. At learning before sleep, performance at an immediate recall was closely comparable between both conditions (hypoglycemic vs. control night 30.2 ± 0.7

Table 1—*Results of neurocognitive tests*

	Type 1 diabetic patients		Healthy subjects		
	Control night	Hypoglycemic night	Control night	Hypoglycemic night	*P* value
Word pairs					
Number of trials	1.31 ± 0.12	1.50 ± 0.13	1.63 ± 0.13	1.63 ± 0.13	NS
Before sleep	28.8 ± 1.1	29.3 ± 0.9	30.4 ± 1.0	31.1 ± 1.0	NS
After sleep	30.6 ± 1.0	30.2 ± 1.3	32.4 ± 1.1	31.1 ± 1.3	NS
Δ	+1.9 ± 1.0	+0.9 ± 0.9	+2.1 ± 0.5	+0.1 ± 0.6	—*†
Word subtest					
Before sleep (s)	45 ± 3	45 ± 2	43 ± 4	44 ± 5	NS
After sleep (s)	45 ± 2	46 ± 2	43 ± 3	44 ± 4	NS
Color subtest					
Before sleep (s)	59 ± 3	55 ± 2	60 ± 4	59 ± 4	NS
After sleep (s)	57 ± 2	58 ± 3	55 ± 4	56 ± 4	NS
Interference subtest					
Before sleep (s)	92 ± 5	81 ± 5	80 ± 4	87 ± 8	NS
After sleep (s)	91 ± 5	79 ± 4	79 ± 5	82 ± 6	NS
ERPs					
P3 A (μV)	13.0 ± 3.2	15.0 ± 2.7	14.0 ± 2.3	12.1 ± 2.2	NS
P3 L (ms)	351 ± 10	332 ± 8	350 ± 11	347 ± 8	NS
N1 A (μV)	−4.9 ± 0.7	−7.3 ± 2.6	−5.35 ± 0.7	−4.96 ± 1.4	NS
N1 L (ms)	117 ± 4	113 ± 3	104 ± 2	114 ± 5	NS
RT (ms)	417 ± 31	416 ± 37	423 ± 31	395 ± 29	NS

Data are means ± SEM. *P* values are derived from ANOVA, including a group factor (type 1 diabetic vs. healthy control subjects) and the repeated-measures factors hypoglycemic (hypoglycemic vs. euglycemic control night) and time (performance before sleep vs. after sleep). Data given for N1 amplitude (A) and latency (L) were recorded at Cz and those for P3 amplitude and latency at Pz. $^*P < 0.05$ for the main effect of time; $^\dagger P < 0.01$ for hypoglycemic × time interaction. Δ, difference between the numbers of recalled word pairs at retrieval testing in the morning and at learning before sleep; RT, reaction time.

vs. 29.6 ± 0.7; $P = 0.45$). Also, the average number of trials to reach the criterion of 60% of correct responses was comparable at learning (1.5 ± 0.9 vs. 1.6 ± 0.9; $P = 0.37$). At retrieval testing in the morning, however, recall performance was significantly impaired after nocturnal hypoglycemia; i.e., average retention was diminished by 1.5 ± 0.5 words after the hypoglycemic night compared with the control night ($P < 0.01$ for hypoglycemia × time). In fact, at retrieval testing after the euglycemic night, subjects correctly remembered 2.0 ± 0.6 more words than in the evening before (31.5 ± 0.8 vs. 29.6 ± 0.7; $P = 0.002$). In contrast, the increase in correctly remembered word-pairs across the hypoglycemic night was marginal (+ 0.5 ± 0.6 words; $P = 0.41$) (Fig. 1*B*). The adverse effect of hypoglycemia on memory performance did not depend on the presence of type 1 diabetes ($P = 0.82$ for time × group and $P = 0.37$ for hypoglycemia × time × group). Also, the hypoglycemia-induced impairment in memory retention in patients with type 1 diabetes did not depend on whether patients were treated with CSII or ICT ($P = 0.14$).

None of the other neurocognitive tests revealed any influence of nocturnal hypoglycemia. Specifically, performance on all subtests of the Stroop test and amplitude and latency of the P3 and N1 components of the ERPs recorded during the auditory vigilance task, as well as reaction times obtained on this task, were very similar at retesting after hypoglycemic and euglycemic control nights (Table 1).

Sleep

Sleep data are provided in the online appendix (available at http://dx.doi.org/10.2337/dc07-0067). Hypoglycemia increased time spent awake during the first part of nighttime sleep ($P = 0.004$). Although this effect of hypoglycemia on sleep was somewhat more pronounced in healthy than in type 1 diabetic subjects, the respective group × hypoglycemia interaction did not reach significance ($P = 0.062$). However, overall healthy subjects spend more time awake during the first part of the night than type 1 diabetic patients ($P = 0.026$). None of the other sleep parameters during the first half of nighttime sleep were affected by hypoglycemia. However, there were differences between the two groups: type 1 diabetic patients spent more time in sleep stage 2 ($P = 0.031$), whereas healthy subjects showed more movements ($P = 0.004$). Sleep during the second half of the night remained completely unaffected.

Correlation analyses

Correlation analyses (for both type 1 diabetic patients and healthy subjects) did not reveal any hint that the impairing influence of hypoglycemia on memory performance was linked to hypoglycemia-induced changes in feelings of fatigue, depression, and restlessness in the morning after sleep. Respective correlation coefficients were as follows: for rated fatigue on the symptom questionnaire, $r = -0.231$ ($P = 0.20$); for fatigue on the adjective checklist, $r = -0.054$ ($P = 0.77$); for depression, $r = -0.114$ ($P = 0.54$); and for inner restlessness, $r = -0.148$ ($P = 0.42$). Also, the hypoglycemia-induced impairment in memory retention was not correlated with the nocturnal cortisol response to hypoglycemia that was determined by the difference between the peak value during hypoglycemia and the corresponding level during the control night ($r = -0.191$; $P = 0.30$) as well as by the respective difference in the area under the curve between the beginning and end of the 1-h hypoglycemic interval ($r = -0.152$; $P = 0.41$). In patients with type 1 diabetes, impaired memory performance did not correlate with A1C level ($r = -0.025$, $P = 0.93$) or disease duration ($r = -0.335$, $P = 0.21$).

CONCLUSIONS — Our data indicate that a short hypoglycemic period during nocturnal sleep, in addition to adversely affecting mood in the next morning, significantly impairs declarative memory consolidation. In contrast, attention and vigilance as assessed by the Stroop test and on an auditory vigilance task including ERP recordings were not impaired after sleep-associated hypoglycemia. This pattern of neurocognitive alterations suggests that nocturnal hypoglycemia selectively disturbs the sleep-related processing of memories that underlies the consolidation of these memories. As no hyperinsulinemic-euglycemic clamps were performed during the control night, we cannot fully exclude the possibility that concurrent hyperinsulinemia contributed to memory impairment. However, previous studies clearly pointing to a beneficial effect of insulin on memory functions render this possibility highly unlikely (32,33). Memory formation comprises acquisition, consolidation, and recall. Although in our study acquisition before sleep was not subject to any influence of subsequent hypoglycemia, our experimental procedure does not allow a clear discrimination between the immediate effects of hypoglycemia on sleep-associated consolidation and postponed effects on later recall, although recall was tested 6–7 h after nocturnal hypoglycemia had ceased. In the morning after hypoglycemia, subjects felt more tired, depressed, and restless, and these subjective changes might have biased retrieval performance, although this assumption is not supported by correlational analyses. Also, none of the other neurocognitive tests point to a globally impairing effect of nocturnal hypoglycemia on neurocognitive functions at the time of recall testing. In particular, the P3 component of the ERP is considered sensitive to the impairing effects of fatigue (34–36) and has also been shown to be a valid indicator of retrieval function (37). Here, P3 amplitudes were closely comparable in the morning after hypoglycemia and control nights. On this background, the decrease in recall of word pairs after nocturnal hypoglycemia very likely derives from a specific, acutely impairing influence of lowered brain glucose on ongoing consolidation processes of declarative memory occurring during sleep.

The mechanism underlying the impairing influence of hypoglycemia on memory consolidation remains to be elucidated. The hippocampus represents a brain structure significantly involved in declarative memory consolidation (20,38). Recent studies in healthy humans have indicated that hippocampal circuitries involved in the acquisition of declarative memory become reactivated during subsequent SWS, suggesting that sleep-associated consolidation relies on reprocessing of recently acquired memories during SWS (39). Moreover, among the different sleep stages, SWS that dominates the early part of the night appears to be most effective in supporting consolidation of hippocampus-dependent declarative memories (40,41). Of importance, the hippocampus is also one of the brain structures highly vulnerable to the detrimental effects of hypoglycemia (42,43). On this background, it can be speculated that hypoglycemia induced early during the night, i.e., during predominant SWS, specifically interferes with ongoing reprocessing of memories in hippocampal networks, thereby preventing proper consolidation. However, as we did not include a control condition in which effects of hypoglycemia during wake retention intervals were assessed,

the hypothesis of an impairment pertaining specifically to sleep-linked consolidation processes remains to be tested. It is of note that hypoglycemia did not substantially decrease SWS in our subjects, excluding that hypoglycemia diminished memory consolidation by decreasing slow oscillatory activity in thalamocortical networks (41,44,45). Hypoglycemia stimulated the release of counterregulatory hormones including cortisol, which is known to suppress sleep-associated consolidation of declarative memories (29,46). However, in the present study, the hypoglycemia-induced decrease in word pair retention was not correlated with indicators of cortisol counterregulation. Thus, the deteriorating effect of hypoglycemia on memory formation does not seem to be primarily mediated by counterregulatory cortisol release.

In contrast to our initial hypothesis of reduced susceptibility of type 1 diabetic patients to the impairing effect of hypoglycemia on memory formation, the hypoglycemia-induced decline in memory consolidation was comparable between patients and healthy control subjects. Notably, a post hoc statistical power calculation indicated that 16 subjects per group were sufficient to detect medium-sized group × hypoglycemic condition interaction effects with a probability of $1 - \beta > 80\%$ (assumed medium effect size $f^2 = 0.0625$), indicating that the lack of differences between the two groups does not reflect a type 1 error. The preserved sensitivity of sleep-dependent memory consolidation to effects of hypoglycemia in type 1 diabetic patients contrasts with findings of decreased sensitivity to nocturnal hypoglycemia in these patients with regard to sleep and hormonal counterregulation (7,8). A growing body of literature indicates that adult patients with type 1 diabetes often manifest mild neurocognitive dysfunctions that are commonly attributed to chronic hyperglycemia and microvascular disease (47). Our findings suggest that repetitive nocturnal hypoglycemia contributes to such mild impairments if they pertain to neurocognitive functions involving the formation of long-term memories. However, it should be noted that the sample size of 16 type 1 diabetic patients precluded the identification of clinical factors such as glycemic control or disease duration that might modulate effects of nocturnal hypoglycemia on memory formation.

The artificially induced hypoglycemia of our study was of rather short duration compared with clinically observed nocturnal episodes of hypoglycemia in type 1 diabetic patients (2–6) so that longer-lasting periods of hypoglycemia during sleep might exert even more pronounced effects. There is some evidence that nocturnal hypoglycemic episodes up to ~100 min do not substantially impair cognitive functions on the following day (14,15). However, with the present study being the first to evaluate impairments of ongoing memory processing by acute hypoglycemia during sleep, it can only be speculated that these impairments are aggravated by increasing duration of sleep-associated hypoglycemia. Also, our results do not allow us to draw any conclusions regarding the long-term consequences of the impairing influence of nocturnal hypoglycemia on memory formation. Previous studies have shown that the enhancing effects on memory of sleep periods as short as 3 h after acquisition can persist for several years (48). Thus, depending on the frequency of nocturnal hypoglycemic events in patients with type 1 diabetes, the impairing influence of sleep-associated hypoglycemia on declarative memory formation observed here indeed may cumulatively affect long-term storage of memory traces in these patients.

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