Hypoglycemia during sleep impairs consolidation of declarative memory in type 1 diabetic and healthy humans

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Kamila Jauch-Chara, MD¹, Manfred Hallschmid, PhD², Steffen Gais, PhD², Sebastian M. Schmid, MD¹, Kerstin M. Oltmanns, MD²,³, Caterina Colmorgen, MD¹, Jan Born, PhD², Bernd Schultes, MD¹,⁴

Internal Medicine I, ²Neuroendocrinology, and ³Psychiatry and Psychotherapy, University of Luebeck, Luebeck, Germany, and from the ⁴Interdisciplinary Obesity Center, Kantonsspital St. Gallen, St. Gallen, Switzerland

Correspondence:
Bernd Schultes, MD
Interdisciplinary Obesity Center
Kantonsspital St. Gallen
Heidenerstr. 11
9400 Rorschach
Switzerland
E-mail: bernd.schultes@kssg.ch

Short title: Memory consolidation after nocturnal hypoglycemia
**Objective:** Early nocturnal sleep enhances the consolidation of declarative memories acquired during prior wakefulness. Patients with type 1 diabetes mellitus (T1DM) 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 Methods:** Sixteen T1DM 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 (ERP) were recorded.

**Results:** Following euglycemia, subjects recalled 1.5 ± 0.5 more word-pairs than following 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 were well comparable between T1DM patients and healthy controls.

**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 T1DM patients prone to nocturnal hypoglycemic episodes and underlines the importance of considering sleep as a critical period in the treatment of these patients.
Hypoglycemic episodes during sleep constitute a particular problem in patients with type 1 diabetes (T1DM), showing incidence rates of up to 56% of nights (1-4). Such episodes can last 1 to 12 h (2-6) and, except for disturbed awakening behaviour (7,8), appear to be frequently asymptomatic (9,10). However, hypoglycemic episodes during nocturnal sleep have been shown to diminish counterregulatory and symptomatic responses to subsequent hypoglycemia (11,12). While 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 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 night-time sleep which is characterized by predominant ‘deep’ slow wave sleep (SWS) enhances the consolidation of declarative memory (19-21). Hence, nocturnal hypoglycemia, especially when occurring during early SWS-rich periods of sleep, may impair the ongoing consolidation of declarative memories. To examine this hypothesis, we induced a short-term hypoglycemia during early night-time sleep in 16 T1DM 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 T1DM 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 T1DM, supposing that the potentially impairing influence on memory consolidation may be less pronounced in T1DM patients than in healthy subjects.

**RESEARCH DESIGN AND METHODS**

**Subjects**

Sixteen T1DM patients (7 women) and 16 healthy control subjects (8 women) matched for age (mean ± SEM, T1DM: 31.3 ± 2.6 yrs, controls: 28.4 ± 1.5 yrs) and body mass index (T1DM: 24.4 ± 0.8 kg/m², controls: 23.0 ± 0.6 kg/m²) participated in the experiments. All subjects had a regular sleep-wake cycle during the four weeks before experiments and were not allowed to take naps during the day before experimental nights. The educational level was well comparable between T1DM patients (8 subjects with high school diploma and 8 subjects with junior high diploma) and healthy controls (9 subjects with high school diploma, 7 subjects with junior high diploma).

Only T1DM patients without diabetic complications were admitted. Mean diabetes duration was 9.1 ± 1.4 years and mean HbA1c was 7.7 ± 0.3 %. Twelve patients were on an intensive conventional therapy (ICT) regime with at least 3 injections of short-acting insulin and 1 to 2 injections of long-acting insulin per day. The remaining 4 patients were on continuous subcutaneous insulin infusion (CSII). The patients on ICT used the following types of insulin: Long-acting insulin: 9 patients - insulin glargine, 2 patients - insulin isophane, 1 patient - prompt insulin zinc suspension (a porcine insulin); short-acting insulin: 6 patients -
regular human insulin, 4 patients - insulin aspart, 2 - patients insulin lispro. All 4 patients on CSII therapy used insulin lispro in their pumps. The study was approved by the local ethics committee. All subjects gave written informed consent prior to participation.

**Study design**

After an adaptation night, each subject was tested on 2 experimental nights spaced at least 2 weeks apart. In one night, hypoglycemia was induced by intravenously infusing insulin (Insuman rapid, Aventis, Bad Soden, Germany). Three minutes after subjects had entered stage 2 sleep (S2) for the first time, insulin infusion was started at a continuous rate of 1.5 mU per kg body weight per min and was continued for 1 hour. Plasma glucose, measured every 5 min (Glucose Analyzer II, Beckman Instruments, Inc., 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. In the control night, euglycemia (> 3.86 mmol/l) was maintained and spontaneous hypoglycemia was prevented by glucose infusion when necessary, which occurred in 5 of the patients’ control nights. The order of experimental conditions was balanced according to a within-subject cross-over 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 previously reported (8).

On each experimental night, subjects went to bed and lights were turned off at 23:00 h. They were woken up at 6:30 h. All neurocognitive tests were performed between 20:30 and 22:15 h in the evening and between 6:30 and 7:30 h in the morning after sleep.

**Sleep recordings and assessment of mood and neurocognitive functions**

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 seconds and an inter-stimulus interval of 100 ms in between. Immediately afterwards, 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 (delta) 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 analyses of variance (ANOVA) including a repeated measures factor ‘hypo’ for the effects of hypoglycemia vs. euglycemia and a repeated measures factor ‘time’ reflecting differences between evening vs. morning. Differences
between T1DM and healthy controls were reflected by a ‘group’ factor. Changes in memory retrieval were expressed as delta values (morning - evening) and subjected to ANOVAs including the repeated measures factors ‘hypo’ and ‘time’. Pair-wise 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, HbA1c and memory performance. A P-value < 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 plasma glucose levels in a linear manner to a nadir level of 2.22 ± 0.01 mmol/l in T1DM 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 (Figure 1A). Due to the insulin infusion, in both T1DM patients (317 ± 116 vs. 1110 ± 162 pmol/l, P = 0.012) and healthy controls (36 ± 8 vs. 1014 ± 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 comparison between T1DM patients and healthy controls; 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 T1DM patients than in the healthy controls.

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) as compared to the control night. Subjects also sensed more coldness (1.13 ± 0.45 vs. 0.38 ± 0.26; P = 0.038) and felt more sweaty (3.00 ± 0.74 vs. 0.88 ± 0.27; P = 0.021). Correspondingly, the results of the adjective check list 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 hypoglycemia night. None of these self-reported alterations depended on whether subjects were diabetic patients or not (P > 0.33 for all comparisons).

Declarative memory and neurocognitive functions
Table 1 summarizes the results of the neurocognitive tests. Patients with T1DM 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 (hypoglycemia vs. control night: 30.2 ± 0.7 vs. 29.6 ± 0.7; P = 0.45). Also, the average number of trials to reach the criterion of 60% of correct responses was well 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 hypoglycemia night in comparison with the control night (P < 0.01 for ‘hypo x 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. 1B). The adverse effect of hypoglycemia on memory performance did not depend on the presence
of T1DM (\(P = 0.82\) for ‘time x group’, and
\(P = 0.37\) for ‘hypoglycemia x time x
group’). Also, the hypoglycemia-induced
impairment in memory retention in patients
with T1DM 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, 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 Appendix 1.
Hypoglycemia increased time spent awake
during the first part of night-time sleep
(\(P = 0.004\)). Although this effect of
hypoglycemia on sleep was somewhat more
pronounced in healthy than in T1DM
subjects, the respective ‘group x
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 T1DM
patients (\(P = 0.026\)). None of the other sleep
parameters during the first half of night-time
sleep was affected by hypoglycemia.

However, there were differences between
the two groups: T1DM 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 (across both T1DM 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, 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
beginning and end of the 1-h hypoglycemic
interval (\(r = -0.152; P = 0.41\). In patients
with T1DM, impaired memory performance
was correlated neither with HbA1c levels (\(r
= -0.025, P = 0.93\) nor with disease duration
(\(r = -0.335, P = 0.21\).

**CONCLUSIONS**

Our data indicate that a short
hypoglycemic period during nocturnal sleep,
besides 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
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 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. While 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 hours
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 correlative analyses. Also, none of the other neurocognitive tests points 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 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 crucially 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). Importantly, 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 interfered with ongoing reprocessing of memories in hippocampal networks, thereby preventing proper consolidation. However, since we did not include a control condition where 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 to note that hypoglycemia did not substantially decrease SWS in our subjects, excluding diminished consolidation due to decreased slow oscillatory activity in thalamo-cortical networks during hypoglycemia (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 T1DM patients to the impairing effect of hypoglycemia on memory formation, the hypoglycemia induced decline in memory consolidation was comparable between patients and healthy controls. Notably, a post hoc statistical power calculation indicated that 16 subjects per group were sufficient to detect medium sized group x hypoglycemic condition interaction effects with a probability of 1-β > 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 T1DM patients stands in contrast to 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 T1DM often manifest mild neurocognitive dysfunctions that are commonly attributed to chronic hyperglycemia and microvascular disease.
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 T1DM patients precluded the identification of clinical factors like glycemic control or disease duration which might modulate effects of nocturnal hypoglycemia on memory formation.

The artificially induced hypoglycemia of our study was of rather short duration in comparison to clinically observed nocturnal episodes of hypoglycemia in T1DM 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 during sleep by acute hypoglycemia, it can only be speculated that these impairments aggravate with increasing duration of sleep-associated hypoglycemia. Also, our results do not allow 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 hours after acquisition can persist for several years (48). Thus, depending on the frequency of nocturnal hypoglycemic events in patients with T1DM, 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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References


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Figure legends

**Figure 1** Plasma glucose concentrations during insulin-induced hypoglycemia (A) and declarative memory performance after hypoglycemic vs. euglycemic control night (B). Plasma glucose levels (mean ± SEM) were measured in 16 healthy subjects (open circles) and 16 patients with type 1 diabetes mellitus (filled circles) during the first 90 minutes after reaching sleep stage 2. An insulin infusion started at the first occurrence of sleep stage 2 (0 min) in order to lower glucose levels to a nadir of 2.2 mmol/l within 60 minutes. 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-paired associate learning task (i.e. recall performance at learning in the evening was subtracted from performance in the morning after sleep) in all subjects (T1DM patients and healthy controls). *P < 0.01