Automated detection of hypoglycemia-induced EEG-changes recorded by subcutaneous electrodes in subjects with type 1 diabetes – the brain as a biosensor

Claus B. Juhl, Kurt Hajlund, Rasmus Elsberg, Mikael Kjer Poulsen, Peter E. Selmar, Jens Juul Holst, Claus Christansen, Henning Beck-Nielsen

1. Introduction

Hypoglycemia is a common and potentially dangerous complication to tight glycemic control in type 1 diabetes patients and is often a limiting factor for further intensification of insulin treatment. The overall rate of severe hypoglycemia in an unselected population of type 1 diabetic patients has been reported to be 0.13 ± 0.10 episodes per patient-year increasing with the duration of diabetes and with intensified treatment. Unawareness, defined as a reduced or abolished ability to sense and respond to hypoglycemia, is a predictor for the risk of severe hypoglycemia. Significant changes in the low frequency range of the electroencephalogram (EEG) appear and disappear within a narrow range of blood glucose concentrations. In pilot studies we have reproduced these findings during insulin-induced graded hypoglycemia using standard scalp electrodes. These data were used to develop a mathematical algorithm that was able to recognize periods of hypoglycemia. However, for the technology to be clinically applicable as a hypoglycemia alarm, it is necessary to use subcutaneously placed electrodes and real-time signal processing.

2. Aim

The aim of the present study is to test the hypothesis (i) that specific changes in EEG can be recorded by the use of subcutaneous electrodes and (ii) that the signals can be processed by a general mathematical algorithm and (iii) that a significant hypoglycemia signal can be detected before the development of clinical hypoglycemia with cognitive failure.

3. Materials and methods

Fifteen type 1 diabetic patients were studied. All patients had a history of symptomatic (N=15) or severe (N=12) hypoglycemia. Exclusion criteria included a medical history of ictal brain seizures and the use of antiepileptic drugs and beta-blocking agents. Four platinum electrodes were implanted subcutaneously (Figure 1A). Hypoglycemia was induced by infusion of glucose-free saline. Plasma glucose was measured every minute and the insulin infusion rate was adjusted to achieve a steady fall in plasma glucose. EEG was recorded throughout the study session. When plasma glucose was three mmol/l and thereafter every five minutes, the cognitive function of the patient was tested by two different tests. The patient was asked to count backwards from a given number between 50 and 100 (correct counting first time: 2 points, correct counting second time: 1 point, unable to count to backwards: 0 points). In addition, the time from significant EEG-changes to severe cognitive loss and the time from significant EEG-changes to severe loss of cognition and to the end of the study was recorded.

4. Results

Patient characteristics are given in Table 1. Eight patients reported partial hypoglycemia unawareness and two patients totally unawareness. Representative examples of hypoglycemia events, corresponding plasma glucose values and the time of significant EEG changes are shown in Figure 2. The EEG changes occurred at the time of significant changes in glucose values. However, there was no correlation between the primary variable and the age of the patient, sex, duration, the overall diabetes regulation as measured by the HbA1c or the rate of glucose fall during the last 15 minutes of the experiment (all p>0.1).

5. Conclusion

The study presents the first steps in the development of an alarm which can be used by type 1 diabetes patients suffering from recurrent hypoglycemia and unawareness. The lead-time from significant EEG changes to severe cognitive dysfunction is, in most cases, long enough for the patient to correct hypoglycemia. The use of subcutaneous electrodes provides an alternative to surface electrodes which makes promises for the development of a device that can be carried during everyday activities.

Conflicts of interest

Kurt Hajlund is a shareholder in Nervus EEG recording System (Iceland). J. Peter Selmar holds stocks in EEG technologies. He is a founder of the Biomedical Research Foundation, a sponsor of Hyposafe A/S. Claus Christansen is CEO in Nordic Bioscience, a sponsor of Hyposafe A/S.

Peter Selmar receives consultant fees from Hyposafe A/S. Claus Christiansen is CEO in Nordic Bioscience, a sponsor of Hyposafe A/S.

References


1. Table 1: Patient characteristics

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<th>Age (years)</th>
<th>Height (m)</th>
<th>Weight (kg)</th>
<th>Duration of diabetes (years)</th>
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2. Table 2: Main variables

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<th>Plasma glucose (mmol/l)</th>
<th>Adrenalin/noradrenalin (nmol/l)</th>
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3. Table 3: EEG recordings during euglycemia (A) and hypoglycemia (B). Increase in delta-amplitude of low frequency scores over time during hypoglycemia is shown in Figure 2. EEG changes were measured using scalp electrodes. Figure 2 illustrates the principle of the mathematical algorithm applied. Each second of EEG recording was subjected to scan-linear spectral analysis. Detection of a significant signal within the predefined spectrum gives rise to an anti-epileptic drug alert and to an event marker, in order to modify the patient’s behavior of awareness. The use of a subcutaneous EEG recording increases the lead-time from significant EEG changes to severe cognitive loss detected by subcutaneous electrodes.

4. Figure 2: Time course of plasma glucose and the mean result of the cognitive tests. In all patients, adrenaline and noradrenalin increased significantly during induced hypoglycemia to values 11 and 2.5 times the basal levels respectively, while only seven subjects were glucagon responders. Figure 3a shows a representative example of EEG during euglycemia (panel A) and during an episode of hypoglycemia (panel B). Representative examples of cumulated hypoglycemia events, corresponding plasma glucose values and the time of significant EEG changes are shown in Figure 4. Table 2 shows the mean plasma glucose at the time of significant EEG changes and at the end of the study. There was no correlation between the primary variable and the age of the patient, sex, duration, the overall diabetes regulation as measured by the HbA1c or the rate of glucose fall during the last 15 minutes of the experiment (all p>0.1).

5. Figure 3: Cumulated hypoglycemia events, corresponding plasma glucose values and the time of significant EEG changes (all p>0.1).

6. Figure 4: Representative examples of cumulated hypoglycemia event (blue line), corresponding plasma glucose values (grey line) and the predefined threshold for significant EEG changes (red line). Three experiments resembled the patient pattern in panel A. Panel B shows the patient with the clinical alarm occurring during a period of recurrent hypoglycemia and without a significant EEG change. The only example of a false positive alarm occurring during a period of recurrent hypoglycemia was in the patient recovering from the episode in panel B. EEG changes were measured using scalp electrodes. The use of a subcutaneous EEG recording increases the lead-time from significant EEG changes to severe cognitive loss detected by subcutaneous electrodes.

8. Figure 5: Representative examples of cumulated hypoglycemia event (blue line), corresponding plasma glucose values (grey line) and the predefined threshold for significant EEG changes (red line). Three experiments resembled the patient pattern in panel A. Panel B shows the patient with the clinical alarm occurring during a period of recurrent hypoglycemia and without a significant EEG change. The only example of a false positive alarm occurring during a period of recurrent hypoglycemia was in the patient recovering from the episode in panel B.