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EEG power and glucose fluctuations are coupled during sleep in young adults with type 1 diabetes

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HIGHLIGHTS

- Glucose and EEG power relationship varies by fluctuation speed during sleep.
- 10–30 min fluctuations in glucose and EEG exhibit brief instances of significant coupling.
- Coupling between glucose and EEG is related to markers of glycemic control and sleep continuity.

ABSTRACT

Objective: To determine the coupling between brain activity and glucose variations during sleep in young adults with type 1 diabetes mellitus (T1DM).
Methods: 27 participants, age 18–30, wore a continuous glucose monitoring system (CGMS) and underwent in-laboratory overnight polysomnography (PSG). Quantitative electroencephalogram (qEEG) metrics were determined from the PSG and included Delta, Theta, Alpha, Sigma, Beta and Gamma Band power at 5-min intervals. Wavelet Coherence Analysis was employed to determine the time varying and frequency specific coupling between glucose and EEG Band power. ANOVA was used to compare differences across fluctuation speeds and EEG bands.
Results: There was a high degree of time varying and frequency specific coupling between glucose variations and EEG power in all EEG Bands during sleep. The average number of intervals of statistically significant coherence was highest for fluctuations periods between 10 and 30 min in all Bands ($p < 0.0001$ for each). Mean significant coherence was negatively correlated with hemoglobin A1c, a marker of glycemic control.
Conclusions: The relationship between glucose and EEG power during sleep is time varying and frequency dependent in young adults with T1DM.
Significance: Understanding the time varying mutual relationship between glucose changes and brain activity during sleep may have implications for disease management in T1DM.

1. Introduction

Accumulating evidence suggests a physiological relationship between sleep and glucose control that is both bi-directional and time varying. This relationship may be of clinical importance for individuals with type 1 diabetes mellitus (T1DM), who rely on administration of exogenous insulin for management of their disease due to autoimmune destruction of pancreatic beta cells. Despite improvements in insulin delivery systems and even with close management, serum glucose levels fluctuate widely in people

Abbreviations: CGMS, continuous glucose monitoring system; HbA1c, hemoglobin A1c; qEEG, Quantitative EEG; T1DM, type 1 diabetes mellitus; WCA, Wavelet Coherence Analysis.

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with T1DM (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, 2010; Ahmet et al., 2011). Such glucose variations may contribute to both the impaired sleep quality (van Dijk et al., 2011) and difficulty returning to sleep after non-severe hypoglycemia (Brod et al., 2012) reported by individuals with T1DM. Further, an association between rapid glucose fluctuations and increased nighttime awakenings has been reported in children with T1DM (Pillar et al., 2003).

Conversely, sleep also plays a role in glucose homeostasis (Hanlon and Van Cauter, 2011). A single night of experimental sleep fragmentation (increased arousals during sleep) or sleep restriction (to 4 h) resulted in decreased insulin sensitivity in healthy adults (Stamatakis and Punjabi, 2009) and in those with T1DM (Donga et al., 2010). Moreover, even during a single night, normal variations in sleep depth are associated with alterations in glucose metabolism. For example, deep sleep is associated with increased growth hormone secretion and decreased insulin sensitivity (Sassin et al., 1969). Despite such evidence, we are aware of no research that has directly characterized the likely bidirectional and time varying interactions between sleep level and glucose in individuals with T1DM.

Using continuous measures of glucose and brain activity, it is possible to characterize the relationship between sleep and glucose in T1DM. Quantitative electroencephalogram (qEEG) analysis provides a continuous measure of brain electrical activity and its distribution over frequencies during the sleep period. Thus qEEG is a useful tool for tracking temporal fluctuations in sleep depth and sleep fragmentation during the night (Nuwer, 1997; Carney et al., 2009). Continuous glucose monitoring systems (CGMS) provide a continuous measure of glucose throughout the night and are commonly employed to monitor glucose levels in people with T1DM (Klonoff, 2005; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, 2010). Wavelet Coherence Analysis (WCA) is a method that permits the assessment of both time varying and frequency specific coupling between two time series (Torrence and Compo, 1998; Grinsted et al., 2004) but has not been applied to studies of glucose homeostasis.

The purpose of this investigation was to characterize the coupling between glucose variations and qEEG measures of brain activity during sleep using WCA in young adults with T1DM. We hypothesized that this coupling would exhibit both time varying and frequency specific characteristics through the night and the relationships identified would vary between EEG Bands.

2. Methods

2.1. Subjects

Thirty young adults, aged 18–30 years, who had been diagnosed with T1DM for at least five years and who used pumps for insulin delivery were enrolled in the study. Exclusion criteria included self-report of: pregnancy; shift-work (night or rotating shifts); use of corticosteroids; diagnosis of primary cardiovascular disease, retinopathy, nephropathy or peripheral neuropathy; diagnosed primary sleep disorder or chronic use of oral sleep medications; use of psychoactive medications (e.g. antidepressants) or illicit drugs (e.g. marijuana or cocaine); or recent history (last 2 months) of severe metabolic instability (e.g. hospitalization for hypoglycemia; occurrence of hypoglycemic seizures or ketoacidosis). Individuals with well-controlled hypertension (systolic pressure <130 mmHg) or thyroid disorder (thyroid stimulating hormone level within normal range) were eligible to participate.

2.2. Study protocol

All procedures were approved by the institutional review board of the University of Illinois at Chicago. Subjects came to the University of Illinois at Chicago for their first visit. After informed consent was obtained and inclusion/exclusion criteria verified, a continuous glucose monitoring sensor (CGMS; Guardian® REAL-Time System, Medtronic MiniMed) was placed in the abdominal subcutaneous tissue, and subjects were instructed in the use of the device. A venous blood sample was collected to measure hemoglobin A1c (HbA1c), a marker of glycemic control. Subjects left the laboratory and spent three days and two nights carrying out normal daily activities (e.g., going to work, normal bed time routine). Subjects were free to exercise and eat ad libitum, and management of their diabetes was not altered during participation in the study. On the third night, subjects returned for overnight polysomnography (PSG) at the Sleep Science Center of the University of Illinois at Chicago while wearing the CGMS. Since subjects had already worn the CGMS for nearly three days prior to the sleep study, they were well adapted to wearing the device. A registered polysomnographic technologist applied the sensors and conducted the PSG study for each subject. PSG testing comprised computer-based recording (Respironics, Alice5®) of: 2 central, 2 frontal and 2 occipital EEG leads, bilateral referential electrooculogram, chin and anterior tibialis electromyogram, lead I electrocardiogram, respiratory movement of thorax and abdomen by piezoelectric strain gauge, airflow via oronasal thermistors and nasal pressure cannula and arterial oxygen saturation of hemoglobin by pulse oximeter. Lights out for each subject was between 10 and 11 pm and lights on was 6 am, ensuring at least 7 h of time in bed.

2.3. Glucose data

The Guardian CGMS included a disposable sensor, a wireless transmitter and a monitor. The sensor, which was inserted into abdominal subcutaneous tissue, sampled glucose levels every 10 s and the average value of these samples was transmitted wirelessly and stored by the monitor every 5-min. The overall system required calibration with a capillary glucose level every 12 h; a procedure performed by the subjects throughout the protocol. The CGMS reports interstitial glucose concentrations between 40 and 400 mg/dl. After each subject completed the protocol, their glucose values were downloaded from the monitor using CareLink® software provided by the manufacturer. Mean overnight glucose and two measures of glucose variability (standard deviation [SD]) were determined from the CGMS.

2.4. EEG data

Six EEG derivations were recorded: two frontal (F3/A2 and F4/A1), two central (C3/A2 and C4/A1) and two occipital (O1/A2 and O2/A1). All EEG signals were lowpass filtered (200 Hz; 6 dB/octave Butterworth filter) and digitized 500 times per second. For analysis purposes, EEG data collected during the PSG starting at the time of lights out were imported into Matlab utilizing the EEGlab plugin (Delorme and Makeig, 2004). For each EEG derivation, we determined power in the Delta (0.5–4.0 Hz), Theta (4.03–8.0 Hz), Alpha (8.03–12.0 Hz), Sigma (12.03–15.0), Beta (13.03–30.0 Hz) and Gamma (30.03–80.0 Hz) Bands according to the recommendations of the International Pharmaco-EEG Society (Jobert et al., 2013). For each 30-s EEG epoch, we demeaned and applied a Hamming window to the 15,000 data points (without zero padding) using a taper of 0.5. We then applied the Discrete Fourier Transformation to obtain the power density periodogram and extracted the power for each Band by numerical integration. For each Band, these values were averaged over 10 consecutive 30-s epochs to provide a