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Original Article

A preliminary study of slow-wave EEG activity and insulin sensitivity in adolescents

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ABSTRACT

Objective: The objective was to evaluate the relationship between the time course of slow wave EEG activity (SWA) during NREM sleep and insulin sensitivity in adolescents.
Methods: Nine normal weight and nine overweight (BMI > 85th percentile) adolescents (13–18 years of age) participated. None of the participants had a history of sleep disordered breathing, confirmed by sleep study. Participants maintained a regularized sleep wake cycle for five days followed by overnight polysomnography in the lab or at home. An oral glucose tolerance test (OGTT) was administered after a 12 h fast and within two weeks of the sleep study. Whole body insulin sensitivity (WBISI) and homeostasis model assessment (HOMA-IR) determined insulin resistance. Power spectral analysis quantified slow-wave EEG activity (.05–3.9 Hz) and exponential regression evaluated SWA across successive NREM periods.
Results: Those who were insulin resistant and had low insulin sensitivity had less Stages 2, 3 and 4 of NREM sleep, more Stage 1, but did not sleep less than those with low resistance and high sensitivity. SWA power was significantly lower in the first NREM period and the decay rate of SWA across NREM sleep was significantly slower in the low insulin sensitivity group. Similar results were obtained after removing the influence of BMI and Tanner score.
Conclusions: Insulin sensitivity in adolescents is related to SWA power and its time course, not total sleep time, regardless of BMI.

1. Introduction

Epidemiological studies have shown that reduced total sleep time is associated with impaired glucose tolerance and an elevated risk for the development of type 2 diabetes in adults [1,2]. Laboratory-based polysomnographic assessments of sleep have confirmed that the incidence of type 2 diabetes was nearly twice as high in those with sleep onset insomnia compared to those with sleep complaints, but no objective evidence of insomnia [3]. Further, the association between insomnia and incidence of diabetes remained after controlling for body mass index (BMI), suggesting that sleep may play a unique role in diabetic risk above that conferred by obesity.

Further, sleep restriction and sleep deprivation produce 30–40% worsening in glucose tolerance and acute insulin response to an oral glucose challenge in healthy adults [4,5]. More recent studies indicate that a single night of partial sleep deprivation results in significant changes in hepatic and peripheral glucose metabolism and peripheral lipolysis [6]. In a similar study, a single night of total sleep deprivation was associated with impaired glucose tolerance in healthy young men that was equivalent to the level of glucose tolerance in non-sleep deprived diabetic men [5].

Using actigraphs to quantify sleep, Gozal and colleagues have shown that short and disrupted sleep in children is associated with high levels of fasting glucose and low levels of insulin sensitivity, low density lipoproteins and elevated C-reactive protein [7,8]. Moreover, children with evidence of sleep disordered breathing or sleep apnea showed the greatest sleep disruption and the strongest evidence of impaired insulin sensitivity [9].

However, van Cauter and colleagues have shown that it is NREM sleep, and specifically delta waves EEG activity, that plays the strongest role in regulating leptin, ghrelin and appetite [5]. Most compelling, reducing delta waves results in a significant increase in glucose tolerance [10]. Since delta waves in NREM sleep, also known as slow-wave activity (SWA) are presumed to be a proxy of homeostatic sleep drive and the recovery function of sleep, SWA measures and assessing the baseline time course of SWA may be more strongly related to insulin sensitivity than sleep duration. To date, however, SWA measures have not been included in these studies and they have been restricted to adults. The purpose of the proposed study was to assess the time course of SWA and its relationship to insulin sensitivity in adolescents.

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The purpose of the present study was to evaluate the relationship between SWA and subsequent insulin sensitivity in adolescents. Our hypothesis was that those with low SWA would be associated with high insulin resistance and low insulin sensitivity.

2. Methods

The study was approved by the Institutional REVIEW Board of the University of Michigan and all participants provided written informed consent (or assent for those under 18 years of age). Twenty 13–18 year olds were recruited for study, but for technical reasons, data were only available for 18 participants (15.5 ± 1.4 years), nine females and nine males. Half of the participants were overweight based on a BMI > 85th percentile [11]. Evidence of sleep disordered breathing by history or polysomnogram was exclusionary, as was current medication use. Tanner maturational development was assessed and all participants were Tanner Stage 3 or higher (4.6 + 0.6).

Subjects were asked to maintain regular sleep/wake sleep schedules for five days prior to study, based on their habitual schedules and confirmed by sleep diary and actigraphy.

Standard polysomnography (PSG) was conducted on a single night in the home ($n = 8$) or in the UM lab ($n = 10$). EEG was recorded from C3 and C4, referenced to the earlobes and connected to a 10-kΩ resistor to minimize nonhomogeneous current flow. The electrode montage also included left and right electrooculogram (EOG) leads placed on both the upper and lower canthi; a bipolar, chin-cheek electromyography (EMG); leg leads, chest and abdomen respiration bands, and a nasal–oral thermistor. Impedances were maintained below 2 kΩ. Records were scored according to Rechtschaffen and Kales [12] standardized criteria by research assistants trained to better than 90% agreement on an epoch-by-epoch basis. Scoring of respiratory events followed the AASM guidelines [13]. Using adult criteria, where apneas were defined as >90% reduction in air flow of at least 10 s duration and hypopneas were defined as a 30% drop in flow of at least 10 s duration, with > 4% desaturation; none of the subjects in the present study had an AHI > 0. In fact, none of the participants showed respiratory events that lasted 20 s or longer and were associated with >3% desaturation. EEG arousal was defined as an abrupt shift to higher frequency of >3 s duration and preceded by >10 s of stable sleep [14].

All electrophysiological signals were transduced by Vitaport III™ described in detail elsewhere [11]. All data were digitized at 256 Hz and analyzed with power spectral analysis (PSA). Although the full EEG spectrum was quantified, statistical analyses for the present paper focused on SWA (0.5 to <4 Hz) power in each successive period of NREM Stage 2, 3, or 4 sleep. Stage 1 sleep epochs were excluded from the SWA analysis and NREM periods were terminated by either REM or wakefulness. In addition, the %SWA power in each NREM period expressed relative to all night SWA power was computed to control for individual differences in overall power. Exponential regression determined the accumulation and decay rate of SWA across the night [15]. High accumulation of SWA in the first NREM periods with rapid dissipation over subsequent NREM sleep time is considered evidence of a strong homeostatic sleep drive.

A two hour oral glucose tolerance test (OGTT) was administered the morning following the sleep study after a 12-h fast in 15/18 subjects. For logistic reasons, the remaining three subjects had OGTTs within two weeks of the sleep study. Plasma glucose and insulin values were assessed at time 0, and 30, 60, 90, and 120 min after the consumption of an oral glucose solution dosed at 1.75 mg/kg up to a max of 75 gm [16].

Two different measures of insulin sensitivity were measured to be consistent with the literature. The whole body insulin sensitivity index (WBISI) was computed using the formula: WBISI = (10,000/square root (glucose at time 0 × insulin at time 0 × average glucose × average insulin)) [13]. The homeostatic model assessment of insulin resistance (HOMA-IR) [17] was computed using the formula HOMA-IR = (insulin at time 0 (microunits per millileter and glucose at time 0 (millimoles per liter)/22.5. To create a categorical between-group variable for insulin and glucose measures, HOMA-IR and WIBISI were split into tertiles. The highest levels of insulin resistance represent the highest tertile on HOMA-IR and the lowest tertile for WBISI. Analysis of variance (ANOVA) assessed the relationship between SWA in each NREMP, and glucose and insulin measures, controlling for age, and BMI percentile. The decay rate of SWA was also compared across tertiles of WBISI and HOMA-IR.

The three subjects who did not have OGTTs in the morning after sleep study were distributed across the tertile of HOMA-IR. The sleep and insulin data were compared to their respective groups to insure that they fell within one standard deviation of the mean.

3. Results

3.1. PSG measures

The means and standard deviations of select polysomnographic variables and HOMA-IR and WBISI values are shown in Table 1, grouped by HOMA-IR tertiles. ANOVA indicated that only the percentage of Stage 1 ($F_{2,15} = 2.9$, $p < .05$) and percentage of Stage 2, 3, 4 ($F_{2,15} = 5.8$, $p < .01$) differed between tertiles. Multiple comparisons indicated that the 1st tertile (insulin resistant) had significantly more Stage 1 and less Stage 2, 3, 4 sleep than the 2nd and 3rd tertiles ($p < .05$). Results were similar with WBISI tertiles, showing significant effects for Stage 1 ($F_{2,15} = 4.1$, $p < .04$) and Stage 2, 3, 4 combined ($F_{2,15} = 5.1$, $p < .02$). Those with the lowest insulin sensitivity had more Stage 1 and less Stage 2, 3, 4 than the middle and highest insulin sensitivity groups (range of p: .02–.003). Note that, total sleep time did not differ by HOMA-IR or WBISI tertile, nor did any of the other PSG measures ($F < 1$).

3.2. SWA measures

The time course of SWA also varied as a function of HOMA-IR and WBISI tertiles. Fig. 1 illustrates the %SWA and its decay over NREM sleep. The decay rate of SWA was significantly slower (−.085) in those with the lowest insulin sensitivity (1st tertile WBISI) and outside the 95% confidence interval of the 2nd (−.15) and 3rd tertile (−.18) groups. The decay rate of SWA did not differ between the middle and high insulin sensitivity groups. Similarly, for HOMA-IR tertiles, those who were the most insulin resistant had the slowest SWA decay rate and were outside the 95% confidence interval of the other two tertiles.

The %SWA power also differed by insulin resistance and sensitivity tertiles as evidenced by a significant NREM period by tertile interaction, (HOMA-IR: $F_{3,48} = 3.0$, $p < .04$; WBISI: $F_{3,48} = 5.2$, $p < .02$, respectively). Multiple comparisons indicated that it was only %SWA in the first NREM period that distinguished between groups. Insulin resistance and low sensitivity was associated with significantly lower %SWA in the 1st NREM period than that observed in either the 2nd or 3rd tertiles ($p < .001$).

As a final set of analyses, the relationship between SWA power and %SWA in the first NREM period and HOMA-IR and WBISI tertiles was also assessed after removing the potential influence of BMI and Tanner score in an ANCOVA model. Removing the influence of BMI, %SWA remained statistically different between insulin resistance and insulin sensitivity tertiles (HOMA-IR: $p < .001$; WBISI: $p < .02$). Similarly, SWA power remained significant after removing BMI (HOMA-IR: $p < .001$; WBISI: $p < .04$).