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Selective slow wave sleep but not rapid eye movement sleep suppression impairs morning glucose tolerance in healthy men

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Summary Shortened nocturnal sleep impairs morning glucose tolerance. The underlying mechanism of this effect is supposed to involve a reduced fraction of slow wave sleep (SWS). However, it remains unanswered if impaired glucose tolerance occurs due to specific SWS reduction or a general disturbance of sleep. Sixteen healthy men participated in three experimental conditions in a crossover design: SWS suppression, rapid eye movement (REM)-sleep disturbance, and regular sleep. Selective sleep stage disturbance was performed by means of an acoustic tone (532 Hz) with gradually rising sound intensity. Blood concentrations of glucoregulatory parameters were measured upon an oral glucose tolerance test the next morning. Our data show that morning plasma glucose and serum insulin responses were significantly increased after selective SWS suppression. Moreover, SWS suppression reduced postprandial insulin sensitivity up to 20%, as determined by Matsuda Index. Contrastingly, disturbed REM-sleep did not affect glucose homeostasis. We conclude that specifically SWS reduction is critically involved in the impairment of glucose tolerance associated with disturbed sleep. Therefore, glucose metabolism in subjects predisposed to reduced SWS (e.g. depression, aging, obstructive sleep apnea, pharmacological treatment) should be thoroughly monitored.

1. Introduction

National surveys in the USA revealed that the average time spent asleep has been reduced by approximately 2 h over the past century (Gangwisch et al., 2007). This is alarming since epidemiological studies indicate a link between habitual short sleep duration and an increased risk of obesity (Cappuccio et al., 2008), arterial hypertension (Gottlieb et al., 2006), cardiovascular disease (Nagai et al., 2010), and the metabolic syndrome in general (Jennings et al., 2007). Specifically, habitual short sleep duration is associated with an increased risk of type 2 diabetes mellitus (DM) (Gottlieb et al., 2005; Gangwisch et al., 2007). Considering the comorbid overweight

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in type 2 DM, it suggests itself that the association between poor sleep and type 2 DM may be due to the body weight-promoting effects of sleep loss because a chronic lack of sleep assumingly fosters the development of obesity (Schmid et al., 2009; Benedict et al., 2011, 2012). This view, however, does not explain why acute and subchronic episodes of sleep loss examined under laboratory conditions impair glucose tolerance even in normal weight volunteers (Spiegel et al., 2005; Buxton et al., 2010; Donga et al., 2010; van Leeuwen et al., 2010).

Beyond the known detrimental effects of sleep time restriction, it has been shown that disturbed sleep quality represents a risk factor for type 2 DM (Stamatakis and Punjabi, 2010; Kita et al., 2012;), which leads to the assumption that a disarranged sleep architecture per se impacts glucose metabolism. In this context, a previous study suggested that subchronic deprivation (i.e., 3 nights) of slow wave sleep (SWS), without sleep time restriction, impairs morning glucose tolerance (Tasali et al., 2008). However, because this study did not involve a comparison condition examining the effects of non-SWS disturbance, the question if general sleep disruption or sleep stage-specific disturbances influence glucose homeostasis remains unsettled.

In order to clarify this question, we aimed to differentiate between the impact of SWS-suppression and disturbed sleep architecture during non-SWS episodes on glucose metabolism under conditions of physiological sleep duration. To this aim, the effects of one night of selective SWS suppression on morning glucose tolerance were compared with those after a night of REM-sleep disturbance and normal sleep as a control condition.

2. Methods

2.1. Study population

Sixteen healthy male volunteers were included into the study [age (mean $\pm$ SEM): 22.1 $\pm$ 0.8 years; body mass index (in kg m^{-2}): 23.2 $\pm$ 0.3]. All subjects had a regular self-reported sleep-wake rhythm for 6 weeks before the experiments and were not on any medication. Sleep disorders were excluded by sleep monitoring during a separate habituation night prior to participation in the sleep laboratory. During the week before each experiment, participants were instructed to go to bed between 2300 h and 2330 h, to get up by 0700 h in the morning, and not to take any naps during the day. Exclusion criteria were chronic or acute illness, current medication of any kind, smoking, alcohol or drug abuse and any circumstances affecting participants' sleep, e.g., high psychological or physical stress. The study conformed to the Declaration of Helsinki and was approved by the Ethics Committee of the University of Luebeck. All subjects gave written informed consent.

2.2. Experimental setting

According to a randomized, balanced cross-over design, each subject participated in three experimental conditions: selective suppression of SWS, disturbance of REM-sleep, and regular sleep. Experimental testings started at 1800 by the preparations for the experimental night until 2300 h, the intervention (2300–0700 h), and the post-intervention period (0700–1330 h). During the entire experimental sessions, strenuous physical stress was strictly avoided. All examinations were separated by at least two weeks.

At arrival in the late afternoon, all participants were in a fasting state and had abstained from drinking calorie- or caffeine-containing beverages for at least 6 h Subsequently, an intravenous catheter was inserted into an antecubital vein of the arm for blood sampling. At $\sim$1900 h, volunteers had a standardized dinner. Afterwards, they were prepared for nocturnal polysomnography, i.e., electrodes were attached to the scalp (electroencephalogram, EEG), around the eyes (horizontal and vertical electrooculogram, EOG), and to the chin (electromyogram, EMG) for standard measurements. In all conditions, lights were turned off at 2300 h and participants were awakened at 0700 h. In the morning after the nocturnal intervention period, all subjects participated in an oral glucose tolerance test (OGTT), i.e., they drank 75 g glucose dissolved in 300 ml water. Before and after the OGTT, blood was repeatedly drawn by intravenous catheter to measure plasma glucose and glucoregulatory hormones (see below).

2.3. Sleep intervention

During the experiments, polysomnographic recordings were performed by using a digital EEG device connected to surface electrodes and were scored in an online modus following standard criteria by Rechtschaffen and Kales (Rechtschaffen and Kales, 1968). Suppression of SWS and REM-sleep disturbance were conducted by acoustic delivery of a standardized tone of 532 Hz, starting at 35 dB This intensity increased automatically in steps of 3 dB every 5 s, reaching a maximum of 62 dB after 45 s as operated by specifically developed software. This stimulation scheme was chosen based on preliminary pilot experiments, which revealed that the acoustic stimulation with a frequency of 532 Hz and an intensity of 35 dB, increasing 3 dB every 5 s, is successful to disturb different sleep stages. The acoustic stimulus was presented by two loud speakers located $\sim$30 cm behind the participant's head. EEG criteria for starting the acoustic stimulus presentation in the SWS condition were defined as follows: $\geq$6 delta waves with an amplitude of $\geq$75 μV and a frequency of $\leq$2 Hz within a 30 s period of sleep time. Tone presentation was immediately stopped by the experimenter whenever $<$6 delta waves occurred and EEG criteria of lighter sleep stages such as spindles, k-complexes, α-waves or arousals were detectable. High care was taken to prevent a waking state.

As an appropriate control condition with a comparable degree of sleep fragmentation acoustic stimulation in the REM-sleep condition was chosen because it is known that the time spent in REM sleep is comparable to the time spent in SWS (Jauch-Chara et al., 2008) but mainly occurs in the second half of the night (Rechtschaffen and Kales, 1968). Start-up criteria for tone presentation in the REM-sleep condition were defined as follows: counterrotating rapid eye movements in combination with low electromyography (EMG) recordings. The tone was immediately stopped when rapid eye movements disappeared and a higher voltage EMG and spindles, k-complexes or arousals occurred. In order to

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