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Endocrine and Metabolic Aspects of Various Sleep Disorders

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Disertační práce bude nejméně pět pracovních dnů před konáním obhajoby zveřejněna k nahlížení veřejnosti v tištěné podobě na Oddělení pro vědeckou činnost a zahraniční styky Děkanátu 1. lékařské fakulty.

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Abstract:
Recent epidemiological and experimental data suggest a negative influence of shortened or disturbed night sleep on glucose tolerance. However, no comparative studies of glucose metabolism have been conducted in clinical sleep disorders. Dysfunction of the HPA axis may play a causative role in some sleep disorders and in other sleep disorders it may be secondary to the sleep disorder. Moreover, dysfunction of the HPA axis is regarded as a possible causative factor for the impaired glucose sensitivity associated with disturbed sleep. However, data on HPA system activity in sleep disorders are sparse and conflicting.

We studied 25 obstructive sleep apnea (OSA) patients, 18 restless legs syndrome (RLS) patients, 21 patients with primary insomnia and compared them to 33 healthy controls. We performed oral glucose tolerance test and assessed additional parameters of glucose metabolism. The dynamic response of the HPA system was assessed by the DEX-CRH-test which combines suppression (dexamethasone) and stimulation (CRH) of the stress hormone system.

Compared to controls, increased rates of impaired glucose tolerance were found in OSA (OR: 4.9) and RLS (OR: 4.7), but not in primary insomnia. In addition, HbA1c values were significantly increased in the same two patient groups. Significant positive correlations were found between 2-h plasma glucose values and the apnea-arousal-index in OSA ($r = 0.56$; $p,0.05$) and the periodic leg movement-arousal-index in RLS ($r = 0.56$, $p,0.05$). Sleep duration and other quantitative aspects of sleep were similar among patient groups.
After HPA axis suppression the number of non-suppressors did not differ among groups. Following CRH stimulation we did not detect differences in ACTH or cortisol levels and adrenocortical responsivity to ACTH was comparable among groups. These results for the first time document normal HPA system feedback sensitivity in various sleep disorders.

Keywords: Sleep, Insomnia, Obstructive sleep apnea, Restless legs syndrome, Glucose metabolism, Oral glucose tolerance test, Hypothalamus-pituitary-adrenal axis, Negative feedback sensitivity, Dexamethasone suppression corticotropin hormone stimulating test

Abstrakt:
Výsledky epidemiologických a experimentálních studií naznačují negativní vliv krátké doby trvání spánku nebo přerušovaného spánku na glukózovou toleranci. Doposud však nebyly provedeny žádné srovnávací studie glukózového metabolismu u klinických spánkových poruch. Dysfunkce HPA osy může hrát stěžejní roli v patofysiologii některých spánkových poruch, u jiných poruch spánku může být sekundární k narušenému spánku. Dysfunkce HPA osy je také považována za možnou příčinu poruch glukózové tolerance spojených s poruchami spánku. Nicméně údaje o funkci HPA osy u spánkových poruch jsou skrovné a konfliktní.

Vyšetřili jsme celkem 25 pacientů s obstrukční spánkovou apnoe (OSA), 18 pacientů se syndromem neklidných nohou (RLS), 21 pacientů s primární insomnií a porovnali je s 33 zdravými kontrolami. Provedli jsme orální glukózový toleranční test (OGTT) a hodnotili další parametry metabolismu sacharidů. Dynamická odezva HPA systému byla hodnocena DEX-CRH-testem, který spojuje supresi (dexametazon) a stimulaci (CRH) HPA osy.

Zaznamenali jsme vyšší výskyt poruch glukózové tolerance u pacientů s OSA (OR: 4.9) a RLS (OR: 4.7) ve srovnání s kontrolní skupinou, nikoli však u primárních insomniaků. Kromě toho byly u těchto dvou skupin pacientů výrazně vyšší hodnoty HbA1c. Statisticky významné positivní korelace jsme nalezli mezi plasmatickou hladinou glukózy 2h po zátěži a indexem počtu probouzecích reakcí vázaných na respirační událost za 1h spánku u OSA (r = 0.56; p,0.05) a indexem počtu probuzení souvisejících s periodickými pohyby končetin za 1h u RLS (r = 0.56, p,0.05). Doba trvání spánku a obdobné polysomnografické parametry se mezi skupinami pacientů nelišily. Po supresi HPA osy se také skupiny neodlišovaly v počtu non-supresorů. Po stimulaci HPA osy jsme nezjistili rozdíly v hladinách ACTH a kortizolu, stejně jako v adrenokortikální responsivitě k ACTH. Výsledky poprvé dokumentují normální sensitivitu zpětné vazby v HPA systému u vybraných spánkových poruch.

Klíčová slova: spánek, insomnie, obstrukční spánková apnoe, syndrom neklidných nohou, glukózový metabolismus, orální glukózový toleranční test, hypotalamo-hypofyzární-nadledvinová osa, negativní zpětná vazba, dexametazonový supresní kortikotropin uvolňující hormon stimulační test

Introduction:

Evidence from well-defined cohort studies has shown that short sleep duration is associated with increased incidence of diabetes (Cappuccio et al., 2010). Laboratory findings in sleep restriction paradigm support results from epidemiologic surveys. Spiegel et al. (1999) published data from young men who underwent sleep restriction of 4h per night for 6 consecutive nights. Glucose clearance was 40% slower in sleep debt condition than in the sleep recovery condition. Glucose effectiveness was 30% lower in sleep debt compare to sleep recovery conditions. The 24-hour cortisol profile was altered too. There were a shorter quiescent period and raised concentrations in the afternoon and early evening. The decrease of free cortisol concentrations in the afternoon and in the evening was about six times slower in the sleep debt condition. This might reflect decreased efficiency of the negative feedback loop. Moreover, dysfunction of the HPA axis is discussed as a possible causative factor for the impaired glucose sensitivity associated with disturbed sleep.

Most research focuses on sleep loss consequences resulting from a behavioral sleep restriction rather than from presence of a sleep disorder.

It is well-documented that obstructive sleep apnea is, independently of BMI and other confounders, associated with glucose intolerance, insulin resistance, and diabetes (Tasali et al., 2008a). On the other hand, there is only one study assessing glucose metabolism in restless legs syndrome (Bosco et al., 2009) and there is not even one study in insomniacs.

There is also paucity of studies assessing HPA activity in insomnia. Insomnia patients with objectively fragmented nighttime sleep show elevated 24-h plasma ACTH and cortisol levels (Rodenbeck et al., 2002) with greatest elevations in the evening and the first half of the night (Vgontzas et al., 2001a). However, insomnia patients showing only minor alterations of sleep exhibited normal cortisol secretion levels (Riemann et al., 2002). Results obtained from studies in sleep disordered breathing are quite inconsistent. In patients with an obstructive sleep apnea syndrome some studies reported enhanced cortisol secretion (Bratel et al., 1999) while other studies did not find alterations in HPA system activity (Dadoun et al., 2007). Noteworthy, several of these studies were limited in that cortisol was measured at a single time point. Finally, four studies assessed HPA axis activity in patients with a restless legs syndrome. Three of them reported normal cortisol profiles and no differences in feedback inhibition (Hornyak et al., 2008) (Garcia-Borreguero et al., 2004) (Wetter et al., 2002) whereas the most recent study focusing on HPA system activity in RLS patients reported enhanced nocturnal cortisol secretion levels (Schilling et al., 2010).

Hypothesis, objectives:

The aim of our study was to assess glucose metabolism by oral glucose tolerance test in three most common sleep disorders – primary insomnia, obstructive sleep apnea and restless legs syndrome. We hypothesized based on abovementioned studies that there is an impaired glucose sensitivity measured with an oral glucose tolerance test in all three sleep disorders due to disturbed sleep from different reasons. We assumed that disturbed sleep per se in primary insomnia as well as fragmented sleep due to upper airway obstruction with concomitant hypoxia in OSA and due to unpleasant sensations in legs and concomitant periodic leg movements in RLS would equally contribute to the supposed impaired glucose sensitivity. We also hypothesized that all three sleep disorders would demonstrate a HPA axis dysfunction, which might be expected to significantly contribute to the disturbed glucose metabolism. We assumed that the putative HPA axis dysfunction might play an important role in primary insomnia and might be interpreted as one the physiological markers of the hyperarousal state, directly contributing to the pathophysiology of insomnia (Vgontzas et al., 2001b). In two other major sleep disorders – obstructive sleep apnea and restless legs syndrome, the potential dysfunction of HPA axis may be secondary due to disturbed sleep due to the sleep fragmentation.

EXPERIMENTAL PART 1: GLUCOSE METABOLISM IN SLEEP DISORDERS

Methods and procedure

The study protocol was approved by the ethics committee of the Bavarian Medical Council, Munich, Germany. All subjects provided written informed consent prior to entering the study. Of 97 subjects investigated, 25 suffered from OSA, 21 from primary insomnia, 18 from RLS and 33 were healthy controls. Subjects were recruited through advertisements in local newspapers. All subjects had normal findings on medical and neurological examination. They did not show any somatic disorder and did not have any severe somatic disorder in the past. All subjects showed normal results in numerous blood tests, including a complete blood count, prothrombin time, activated partial thromboplastin time, fibrinogen, bilirubin, aspartate aminotransferase (AST/ GOT) and alanine aminotransferase (ALT/GPT), gama-glutamyltransferase (GMT/GGT), lactatdehydrogenase, cholinesterase, amylase, lipase, triglycerides, cholesterol, HDL-cholesterol, LDL-cholesterol, total protein, albumin, transferrin, ferritin, iron, C- reactive protein (CRP), thyroid stimulating hormone (TSH), free thyroxine, free triiodthyronine, cortisol levels, creatinine, urea, uric acid, potassium, sodium, calcium, chloride, magnesium, phosphate, and protein electrophoresis. The urine analysis and urine toxicology screen were obtained. Participants did not suffer from any psychiatric disorder and did not have any psychiatric disease in the past. All subjects had a regular sleep-wake cycle. Subjects showing a shift of more than 2 hours during 8 days of wrist actigraphy were excluded. Pregnant women, shift workers and persons who had travelled across multiple time zones within 3 months prior to the study were excluded. Similarly, subjects showing other sleep disorders were excluded. All subjects showed normal EEG and ECG findings during waking.

RLS patients met the diagnostic criteria defined by the International Restless Legs Syndrome Study Group (Allen et al., 2003) and did not suffer from any somatic condition known to cause secondary RLS, such as polyneuropathy. The severity of RLS was assessed using the International Restless Legs Syndrome Study Group Rating Scale (IRLS; Walters et al., 2003). In patients suffering from primary insomnia as well as in patients suffering from OSA, diagnosis was based on the International Classification of Sleep Disorders, 2nd edition (American Academy of Sleep Medicine 2005). OSA patients with an apnea-hypopnea-index (AHI) above 15 (moderate sleep apnea) were included. Controls did not suffer from any sleep disturbances, and sleep related breathing disorder was excluded (AHI > 5) by an ambulatory sleep apnea screening (Weinmann Somnocheck, Hamburg, Germany).

Before entering the study, subjects underwent a detailed screening including a physical examination, anthropometric measurements, a survey of sleep history and a detailed medical and psychiatric interview by an experienced psychiatrist including the Beck Depression Inventory (BDI; Beck et al., 1961), Hamilton Depression Scale (HAMD; Hamilton 1960) and Hamilton Anxiety Scale (HAMA; Hamilton 1959). Probands fulfilling DSM criteria of any mental disorder were excluded from the study. In addition, sleep quality was evaluated by means of the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) and daytime sleepiness using the Epworth Sleepiness Scale (ESS; Johns 1991). To verify regular sleep-wake patterns, participants were asked to wear a wrist activity monitor (Cambridge Neurotechnology, Cambridge, UK; Actiwatch Activity Analysis, Version 5.06) in connection with a sleep diary for 8 days prior to the study. In all patients standard nocturnal polysomnography (PSG) was conducted for two nights. Polysomnographic recordings were performed from 23:00 to 06:00 h including monitoring of the electroencephalography (EEG) in two derivations (C4-A1 and C3-A2), electrooculogram, submental electromyogram (EMG), the right and left anterior tibialis surface EMG, electrocardiogram (ECG), thoracic and abdominal belts, nasal airflow, finger oximetry, microphone and video monitoring. Sleep stages were scored according to Rechtschaffen & Kales (1968). Sleep stages 3 and 4 were summed up to slow-wave sleep. Arousals (American Sleep Disorder Association 1992), PLMS (American Sleep Disorder Association, 1993), and apneas/hypopneas were scored and the number of both PLMS and apneas/hypopneas per hour of total sleep time (PLMS-index and AHI, respectively) was calculated. Additionally, we calculated the number of both PLMS and apneas/hypopneas associated with arousals (PLMS-arousal-index and apnea-arousal-index, respectively). Sleep stages and associated parameters were scored by two experienced scorers in each individual.

After the first night in the sleep laboratory subjects underwent a 4-hour oral glucose tolerance test (OGTT). All OGTTs were performed at 08:00 a.m. after an overnight fast. Fasting samples to assess glucose, insulin, and HbA1c were taken at baseline. After an oral standard load of 75 g glucose, blood samples were taken at 30, 60, 120, 180 and 240 minutes. Glucose was immediately measured using the glucose oxidase method (Synchrone DXC 800 1+2, Beckmann Coulter, USA) with an inter-assay coefficient of variation (CV) of 1.0–2.2% (DXC1) and 1.4–2.2% (DXC2). Insulin samples were measured by using an ELISA (BioSource, Germany) with an inter-assay CV of 4.2%. HbA1c measurement was based on the assessment of total Hb using the colorimetric method, the A1c concentration was determined by means of the turbidimetric immuno-inhibition method (Synchrone DXC 800 1, Beckmann Coulter, USA) with a inter-assay CV of 2.9–3.2%. Standardized to the NGSP reference range was set at 4.3–5.8%.

According to the diagnostic criteria of the American Diabetes Association (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 2003) we defined:

- normal glucose tolerance (NGT). as 2-hour plasma glucose (2h-PG) concentrations < 140 mg/dl (plasma glucose concentration 2 h after an oral glucose challenge)
- impaired glucose tolerance as 2h-PG values ≥140 mg/dl
- diabetes as 2h-PG ≥ 200 mg/dl

The total areas under the curve for glucose (AUCg) and insulin (AUCi) were calculated using the linear trapezoidal rule (Wolever and Jenkins, 1986). The combination of elevated HbA1c values (> 5.5%) and impaired fasting glucose values (FPG > 100 mg/dl) was assessed as an additional risk factor for the development of type 2 diabetes, since several studies have shown that the combination of these parameters is a stronger predictor for the risk of developing type 2 diabetes than increased fasting glucose alone (Ko et al., 2000) (Inoue et al., 2008).

Insulin resistance was assessed using the homeostasis model assessment (HOMA-IR). Homeostasis model assessment (HOMA), originally described by Matthews et al. (1985), is a method for assessing beta-cell function and insulin resistance (IR) from basal (fasting) glucose and insulin or C-peptide concentrations. The model is nonlinear, but can be simply approximated. The model highly correlates with estimates assessed by euglycemic-hyperinsulinemic clamp. Two types of HOMA scores are currently used in clinical practice for determining fasting glucose and insulin levels:

Insulin resistance:
International formula:
HOMA-IR = [Fasting plasma glucose in mmol/l] * [Fasting insulin in mU/L] / 22.5

Beta-cell function:
International formula:
HOMA-Beta = 20 * [Fasting insulin in mU/L] / ([Fasting plasma glucose in mmol/l] - 3.5) %

To encompass both hepatic and peripheral insulin (primarily muscle) sensitivity we calculated a composite measure of whole body insulin sensitivity, ISI-composite or Matsuda index recommended by Matsuda and DeFronzo (1999). Index of whole-body insulin sensitivity represents the combined effect of insulin to stimulate peripheral glucose uptake and to suppress endogenous glucose production. Index correlates with the direct measure of insulin sensitivity derived from the euglycemic insulin clamp.

ISI-composite was calculated using the following formula:

$$ISI_{(Matsuda)} = \frac{10000}{\sqrt{G_0 \times I_0 \times G_{mean} \times I_{mean}}}$$

G_0 fasting plasma glucose

I_0 fasting plasma insulin

G_{mean} mean OGTT glucose concentration

I_{mean} mean OGGT insulin concentration

Statistical Analysis

Statistical analysis was performed using SPSS for Windows 16.0 (SPSS Inc., Chicago, Illinois). Using Gabriel- or Games Howell corrected analysis of variance (ANOVA) tests we compared the mean values of the basic characteristics age, BMI, PSQI and ESS among the four groups. Because of their skewed distribution, HbA1c, FPG, 2h-PG, fasting plasma insulin (FPI), the area under the curve for glucose (AUCg) and the area under the curve for insulin (AUCi) were z-transformed. On metabolic parameters analysis of covariance (ANCOVA) was conducted with the BMI as covariate. A chi-square test was performed to compare the incidence of IGT and/or combined elevated HbA1c and FPG values between groups. After constructing 2x2 contingency tables odds ratios (OR) were calculated. First-order partial correlation and bivariate correlation, respectively, were done to determine the association between continuous variables. $P<0.05$ was considered as statistically significant.

Results

The baseline characteristics for all subjects are shown in Table 1. Groups did not differ with respect to age. As expected, OSA patients had a strongly increased BMI, whereas the BMI of RLS and insomnia patients did not differ from controls. RLS patients suffered from a severe restless legs syndrome (IRLS, 22,9 ± 5,4). OSA patients were all males, yielding a statistically significant gender difference between groups. RLS and primary insomnia patients, however, did not show gender distributions different from controls. Daytime sleepiness (ESS) was highest in OSA patients and did not differ in the other patient groups from controls. In contrast, night sleep was subjectively impaired in all three patient groups compared to controls as assessed by the PSQI, and insomniacs rated their sleep significantly worse than did OSA and RLS patients.

Table 1. Baseline characteristics of study participants

	OSA	RLS	INS	CON	P-value
Females/Males	0/25 ‡ ∇	11/7	12/9	17/16	< 0.001
Age (years)	52.3 (10.8)	52.2 (13.0)	49.1 (9.7)	46.8 (7.7)	> 0.05
BMI (kg/m^2)	32.9 (5.4) ‡	25.4 (3.7)	25.0 (4.8)	24.7 (3.5)	< 0.001
PSQI	6.7 (2.8) ‡ ∇	9.3 (4.5) ‡ $^+$	13.1 (3.7) ‡	3.0 (2.0)	< 0.001
ESS	11.2 (5.6) ‡	7.9 (4.3)	6.4 (4.0)	6.8 (2.8)	< 0.001
BDI	5.4 (3.9) †	7.8 (6.0) †	8.7 (5.6) ‡	2.3 (2.5)	< 0.001
HAMD	2.2 (2.7) * ∇	4.4 (4.0) †	7.3 (2.8) ‡	0.6 (1.2)	< 0.001
HAMA	3.6 (3.3) * ∇	6.3 (5.9) *	10.24 (5.2) ‡	1.5 (1.8)	< 0.001

Data are mean (SD). Statistical comparison was done using Gabriel- or Games-Howell-corrected oneway ANOVA.

OSA, Obstructive sleep apnea; RLS, Restless legs syndrome; INS, Insomnia; CON, Controls; BMI, Body mass index; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; BDI, Becks depression inventory; HAMD, Hamilton depression scale; HAMA, Hamilton anxiety scale.

* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$, vs controls

$^+$ $p < 0.05$, $p < 0.01$, ∇ $p < 0.001$, between groups

OSA: $\chi^2(1) = 18.21$, $p < 0.001$; RLS: $\chi^2(1) = 0.433$, $p > 0.05$; INS: $\chi^2(1) = 0.163$, $p > 0.05$, vs controls

OGTT data indicated that no control and no primary insomnia patient, but four OSA patients and one RLS patient suffered from diabetes. As shown in Table 2, 12% of the controls showed 2h-PG values indicating an impaired glucose tolerance. This rate was significantly increased in OSA (40%, OR 4.9) and RLS (39%, OR 4.7) patients, but not in primary insomnia (18%, OR 1.6) patients. The rate of impaired glucose tolerance within groups was not gender dependent.

Table 2. Frequency of patients with normal glucose tolerance (2h-PG ≤ 140mg/dl) or impaired glucose tolerance (2h-PG ≥ 140mg/dl)

	Total	Normal glucose tolerance	Impaired glucose tolerance	Odd ratios
	N	N (%)	N (%)	
OSA	25	15 (60)	10 (40)	4.9
RLS	18	11 (61)	7 (39)	4.7
INS	17	14 (82)	3 (18)	1.6
CON	32	28 (88)	4 (12)	

OSA, Obstructive sleep apnea; RLS, Restless legs syndrome; INS, Insomnia; CON, Controls.

$\chi^2(3) = 7.95$, $p < 0.05$.

As shown in Table 3, mean HbA1c values were in the normal range (below 5.8%), but differed significantly between groups after adjustment for the BMI. A Sidak-corrected post-hoc test based on estimated marginal means revealed that OSA as well as RLS patients had significantly higher HbA1c values than healthy controls. In both OSA and RLS patients the rate of patients displaying elevated HbA1c and FPG was significantly increased.

Table 3: Frequency of patients with normal and elevated HbA1c (≥ 5.5%) and FPG (≥ 100 mg/dl)

	Total	Normal HbA1c&FPG	Elevated HbA1c&FPG	Odd ratio
	N	N (%)	N (%)	
OSA	25	11 (44)	14(56)	20.0
RLS	17	11 (65)	6 (35)	8.5
INS	19	18 (95)	1 (5)	0.8
CON	33	31 (94)	2 (6)	

OSA, Obstructive sleep apnea; RLS, Restless legs syndrome; INS, insomnia; CON, controls; FPG, Fasting plasma glucose.
$\chi^2(3) = 25.31$, $p < 0.001$.

Accordingly, 56% of the OSA (OR 20.0) and 35% of the RLS (OR 8.5) patients belonged to the high risk group for developing type 2 diabetes. In contrast, only 5% of the insomniacs (OR 0.82) and 6% of the controls showed elevated HbA1c plus FPG levels (see Table 4).

Table 4: Metabolic parameters

	OSA	RLS	INS	CON	BMI adjusted *P* value
HbA1c (%)	5.6 (0.4) †	5.5 (0.3) †	5.3 (0.3)	5.2 (0.3)	< 0.01
FPG (mg/dl)	110.9 (15.6)	100.4 (10.1)	98.8 (8.9)	96.0 (8.0)	> 0.05
FPI (µl/ml)	16.2 (10.5)	8.7 (3.2)	10.3 (5.4)	8.9 (3.3)	> 0.05
2h-PG (mg/dl)	139.0 (55.7)	121.1 (40.8)	120.2 (17.8)	109.5 (23.5)	> 0.05
2h-PI (µl/ml)	82.5 (67.3)	60.0 (67.8)	50.6 (21.3)	36.8 (29.2)	> 0.05
AUCg(mg/dl)	31882 (7592)	28063 (5748)	28369 (3500)	25859 (4014)	> 0.05
AUCi (µl/ml)	15024 (9396)	9873 (6921)	8437 (3588)	8307 (5258)	> 0.05
HOMA1-IR	4.7 (3.8)	2.2 (1.0)	2.5 (1.3)	2.1 (0.9)	> 0.05
ISIcomposite	3.1 (1.6)	6.3 (5.4)	5.1 (1.5)	5.5 (1.9)	> 0.05

Data are mean (SD). Statistical comparison was done using ANCOVA.
OSA, Obstructive sleep apnea syndrome; RLS, Restless legs syndrome; INS, Insomnia; CON, Controls; FPG, Fasting plasma glucose; FPI, Fasting plasma insulin; 2h-PG, 2h-Postload glucose; 2h-PI, 2h-Postload insulin; AUCg, Area under the curve for glucose; HOMA1-IR, Homeostasis model assessment-1 of insulin resistance; ISIcomposite, Insulin sensitivity index composite.
* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$.

Table 5. Sleep parameters

	OSA	RLS	INS	P-value
TIB (min)	437.5 (33.1)	449.2 (32.8)	435.7 (25.8)	> 0.05
TST (min)	339.0 (58.7)	345.9 (69.5)	337.3 (55.6)	> 0.05
SEI (%)	77.5 (11.8)	77.1 (14.6)	77.2 (10.8)	> 0.05
WASO (min)	75.7 (42.8)	75.3 50.1)	61.0 (35.6)	> 0.05
REM (min)	41.4 (18.5) ‡	73.0 (24.1)	70.8 (27.2)	< 0.001
S1 (min)	92.2 (40.2) ‡	41.8 (20.0)	31.3 (14.5)	< 0.001
S2 (min)	198.0 (47.9)	204.2 (47.9)	214.9 (39.5)	> 0.05
SWS (min)	7.4 (9.5) †	26.9 (29.1)	20.4 (17.5)	< 0.01
SO (min)	21.2 (20.9)	22.3 (33.2)	22.4 (19.6)	> 0.05
SLREM (min)	137.7 (68.4) *	97.5 (72.8)	86.4 (46.9)	< 0.05
SLSWS (min)	122.8 (104.9) *	67.9 (92.6)	37.3 (26.0)	< 0.05
AHI	55.7 (27.1) ‡	3.3 (3.7)	1.6 (1.6)	< 0.001
ODI	43.6 (29.7) ‡	1.9 (3.0)	1.4 (1.6)	< 0.001
PLMS-Index	19.2 (20.4)	32.5 (33.1)	5.2 (7.2) †	< 0.01
Arousal-Index	60.2 (23.4) ‡	29.6 (16.0)	24.5 (15.0)	< 0.001
PLMS-arousal-index	12.8 (14.0)	14.8 (15.3)	2.8 (4.7) †	< 0.01
Apnea-arousal-index	33.8 (25.6) ‡	0.8 (1.8)	0.3 (0.5)	< 0.001

Data are mean (SD). Mean comparison was done using Gabriel- or Games-Howell-corrected oneway ANOVA.
OSA, Obstructive sleep apnea; RLS, Restless legs syndrome; INS, Insomnia; CON, Controls; TIB, Time in bed; TST, Total sleep time; SEI, Sleep efficiency; WASO, Wake time after sleep onset; REM, Rapid eye movement sleep; S1, Stage 1 sleep; S2, Stage 2 sleep; SWS, Slow wave sleep; SO, Sleep onset latency; SLREM, REM sleep latency; SLSWS, SWS sleep latency; AHI, Apnea-hypopnea-index; ODI, Oxygen-desaturation-index; PLMS-Index, Periodic leg movements per hour of sleep; PLMS-arousal-index, PLMS associated with arousals per hour of sleep; Apnea-arousal-index, Apneas and/or hypopneas associated with arousals per hour. * $p < 0{\cdot}05$, † $p < 0{\cdot}01$, ‡ $p < 0{\cdot}001$.

Patient groups did not differ significantly in TST, sleep efficiency and WASO. OSA patients showed less SWS and REM sleep, but more stage 1 sleep than both other patients groups. Due to the selection criteria of the present study, only OSA patients showed pathological AHI and oxygen desaturation index. Mean PLMS arousal indices were in the pathological range in OSA and RLS patients, but not in insomnia patients (Table 5). Tasali et al. (2008b) have shown that SWS suppression induced by acoustic stimulation triggering repetitive microarousals leads to a decrease in insulin sensitivity. Because OSA and RLS are characterized by repeated arousals due to apneas and PLMS, we assessed whether they were related to those metabolic parameters differing between patient groups. 2h-PG values correlated positively with the apnea arousal-index ($r=0.56$, $p<0.05$) and the ODI ($r=0.59$, $p<0.05$) in OSA, and with the PLMS-arousal-index ($r=0.56$, $p<0.05$) in RLS. HbA1c correlated positively with the apnea-arousal-index ($r=0.50$, $p<0.05$) in OSA, which was neither the case for the ODI ($r=0.46$, $p<0.05$), nor for the PLMS-arousal-index ($r=0.21$, $p<0.05$) in RLS.

EXPERIMENTAL PART 2: HYPOTHALAMO-PITUITARY-ADRENAL AXIS IN SLEEP DISORDERS

Method and procedure:

Ten days before the PSG nights took place subjects underwent the dexamethasone suppression/corticotropin-releasing-hormone stimulation test (DEX-CRH-test). This test is a dynamic test which combines suppression and stimulation of the HPA system. A week prior the test the subjects had a regular sleep wake cycle without any sleep deprivation, there were no other medical procedures, no diet, no medication or no excessive physical activity. At 23:00 subjects received a single dose of 1.5 mg dexamethasone (Fortecortin, Merck Pharma GmbH, Darmstadt, Germany). On the following day, an indwelling catheter was inserted into antecubital vein. The subjects rested in a supine position. The baseline sample, which represents the suppressive effects of dexamethasone, was drawn at 15:00. At 15:02, 100 µg human CRH (Ferring Inc., Kiel, Germany) reconstituted in 1 ml 0.02% HCl in 0.9% saline solution was infused within 30s. After hCRH infusion four blood samples were taken at 15:30; 15:45; 16:00 and at 16:15. Blood samples were stabilized with Na-EDTA (1mg/ml) and aprotinin (300kIU/ml) and centrifuged at 4C (7 min at 2600g). Plasma was aliquoted and immediately frozen to -20C. Cortisol plasma concentrations were analyzed using a radioimmunoassay kit with a coated tube technique. For ACTH measurements a dual antibody immunoradiometric assay without extraction was used.

The mean plasma hormone concentration, after dexamethasone application, but prior the CRH injection is reported as basal concentration. This concentration reflects the suppressive effect of dexamethasone. Subjects showing basal cortisol concentration ≥ 40ng/ml (e.g. 110 mmol/l) were identified as non-suppressors. The maximal hormone response after CRH administration is reported as peak value and corrected for baseline it is reported as delta. Following hCRH infusion, cortisol and ACTH responses were calculated as the area under the time course curve (AUC) using trapezoidal rule (Wolever and Jenkins, 1986). They are reported as AUC_{total} (not baseline-corrected) and AUC_{net} (baseline-corrected). Finally, adrenocortical responsivity to ACTH is assessed by calculating two pituitary-adrenal ratios (PAR; AUC_{total} ACTH / AUC_{total} cortisol values and AUC_{net} ACTH / AUC_{net} cortisol values).

Statistical analysis

Statistical analysis was performed using SPSS for Windows 16.0 (SPSS Inc., Chicago, Illinois). Mean comparisons of the basic characteristics such as age, BMI, PSQI, ESS, BDI, HAMD and HAMA as well as of the calculated parameters obtained by the DEX-CRH-test were done by using Gabriel- or Games-Howell-corrected analysis of variance (ANOVA) tests.

Because of their skewed distribution HAMD and HAMA were z-transformed. Chi-square tests were performed to compare the number of non-suppressors between groups. Bivariate correlations were done to determine association between selected continuous variables. $P < 0.05$ is considered as statistically significant.

Results

The baseline characteristics for all subjects are shown in Table 1 (shown in Glucose metabolism part). Groups did not differ with respect to age. The OSA group exclusively comprised males; however, the other groups did not differ in means of gender distribution. OSA patients had a strongly increased BMI, whereas in RLS, insomniacs and controls the BMI was comparable. Sleep disorder groups, in particular insomniacs, showed higher scores in the self-rated questionnaire BDI as well as the observer-rated questionnaires HAMD and HAMA than controls. RLS patients, on average, suffered from a severe restless legs syndrome (IRLS, 22.9 ± 5.4). All patient groups described their sleep of poor quality (PSQI) and insomniacs rated their night time sleep worse than did OSA or RLS patients. However, only OSA patients complained about increased daytime sleepiness (ESS).

Patient groups did not differ in respect to sleep efficiency and polysomnographic measured total amount of sleep or awakenings during sleep. OSA patients spent less time in SWS and REM sleep but more in stage 1 sleep compared to RLS and insomnia patients. Due to the selection criteria of the present study OSA patients showed an AHI of 55.7 (± 27.1) and an oxygen desaturation index of 43.6 (± 29.7). PLMS-arousal index was in a pathological range for RLS and OSA patients (Table 5 shown in Glucose Metabolism part).

DEX-CRH data did not indicate differences in the number of non-suppressors between patient groups and controls. 4% of OSA, 12% of RLS and 14% of insomnia patients showed elevated basal cortisol levels. In controls 9% were found to be non-suppressors (Table 3).

Table 3. Frequency of dexamethasone suppressors and non-suppressors

	Total	Suppressors	Non-suppressors
	N	**N (%)**	**N (%)**
OSA	25	24 (96)	1 (4)
RLS	18	16 (88)	2 (12)
INS	21	18 (86)	3 (14)
CON	33	30 (91)	3 (9)

Suppressors: Basal cortisol values < 40 ng/ml; Non-suppressors: Basal cortisol levels ≥ 40 ng/ml.

OSA, Obstructive sleep apnea; RLS, Restless legs syndrome; INS, Insomnia; CON, Controls.

$\chi^2(3) = 7.95$, $p > 0.05$.

In RLS patients, the levels of ACTH after HPA axis suppression by dexamethasone was significantly lower compared to healthy controls. Basal cortisol levels were comparable between groups. The amount of cortisol and ACTH released after hCRH infusion did not differ between groups. Thus, groups show similar values of peak- , DELTA- , AUC_{total} and AUC_{net} levels in cortisol- and ACTH release (Table 4 and Table 5). Furthermore no group differences in adrenocortical responsiveness to ACTH (PAR_{total}; PAR_{net}) were found (Table 4).

Table 4. Cortisol values in ng/ml obtained by the DEX-CRH test

	OSA	RLS	INS	CON	P-value
Basal	17.5 (9.0)	19.1 (11.6)	20.6 (12.8)	21.7 (16.1)	> 0.05
Peak	50.0 (46.7)	51.0 (42.3)	64.2 (56.1)	70.5 (66.8)	> 0.05
Delta	32.4 (44.8)	31.8 (38.6)	43.6 (52.1)	48.6 (58.4)	> 0.05
AUCtotal	2651.8 (2385.3)	2554.2 (2107.2)	3085.8 (2606.6)	3422.1 (3440.8)	> 0.05
AUCnet	1339.6 (2243.9)	1121.3 (1731.6)	1543.6 (2196.2)	1775.8 (2734.8)	> 0.05
PARtotal	0.325 (0.2)	0.227 (0.1)	0.320 (0.2)	0.315 (0.2)	> 0.05
PARnet	0.094 (1.0)	- 0.367 (2.2)	- 0.044 (0.9)	1.512 (5.1)	> 0.05

Data are mean (SD). Statistical comparison was done using Gabriel- or Games-Howell-corrected oneway ANOVA.

OSA, Obstructive sleep apnea; RLS, Restless legs syndrome; INS, Insomnia; CON, Controls; Basal, basal cortisol concentration after DEX; Peak, Highest cortisol value after CRH; Delta, Baseline corrected peak value; AUCtotal, Area under curve; AUCnet, Baseline corrected area under curve; PARtotal, Pituitary-adrenal ratio; PARnet, Baseline corrected pituitary-adrenal ratio.

Table 5. ACTH values in pg/ml obtained by the DEX-CRH test

	OSA	RLS	INS	CON	P-value
Basal	2.1 (2.7)	1.1 (0.2) *	2.7 (3.5)	4.2 (6.6)	< 0.05
Peak	16.5 (14.8)	10.1(9.7)	15.0 (11.5)	15.1 (11.2)	> 0.05
Delta	14.3 (13.4)	9.1 (9.5)	12.2 (10.0)	10.7 (11.1)	> 0.05
AUCtotal	829.2 (767.2)	531.9 (543.0)	790.0 (665.6)	790.1 (605.4)	> 0.05
AUCnet	670.3 (651.7)	452.0 (528.8)	590.0 (539.7)	465.0 (580.8)	> 0.05

Data are mean (SD). Statistical comparison was done using Gabriel- or Games-Howell-corrected oneway ANOVA.

OSA, Obstructive sleep apnea; RLS, Restless legs syndrome; INS, Insomnia; CON, Controls; Basal, Basal ACTH concentration after DEX; Peak, Highest ACTH value after CRH; Delta, Baseline corrected peak value; AUCtotal, Area under curve; AUCnet, Baseline corrected area under curve.

* $p < 0.05$, vs controls

Discussion

Our glucose metabolism study for the first time compared glucose metabolism in various sleep disorders. The major finding is an increased rate of impaired glucose tolerance in patients with OSA and RLS, but not in patients with primary insomnia, as compared to normal controls.

Both RLS and OSA patients were almost five times more likely to suffer from impaired glucose tolerance than healthy controls. In addition, mean HbA1c values were increased in both diagnostic groups compared to controls, and the rate of values above the reference level in both HbA1c and fasting plasma glucose levels indicated an increased diabetes risk in patients with OSA (20-fold) and RLS (9-fold), respectively.

The control group was not matched to the OSA group with respect to gender. Indeed OSA patients were exclusively males. Most population based studies have found a 3-fold higher prevalence of sleep apnea in males then in females (Punjabi, 2008). The ratio of men to women diagnosed in sleep center is even more skewed toward men, with reported ratios 8 : 1 and higher (Ye et al., 2009). Also sex differences in clinical manifestation are described; women in general suffer from less severe disease and report more frequent non-specific symptoms. Since obstructive sleep apnea patients recruited in the study had a full clinical picture of severe obstructive sleep apnea syndrome, we were unable to find women with the same clinical picture. Hence, the present results should, as far as OSA is concerned, be replicated in a gender-mixed patient group compared to gender-matched controls.

Impaired glucose tolerance and increased rates of diabetes have been frequently shown in patients with OSA (Tasali et al., 2008a) and might be related, to a great extent, to obesity, which was also documented in the present study by an increased BMI in this patient group. However, some studies suggest that OSA is related to type 2 diabetes independently of obesity. (Reichmunth et al., 2005) In a large cross-sectional analysis of a subset of data from the Sleep Heart Health Study, involving over 2500 non-diabetic individuals, the presence of OSA was associated with significantly higher odds of impaired fasting glucose and impaired glucose tolerance after controlling for age, sex, race, BMI, and waist circumference. Importantly, the magnitude of these associations was similar in non-overweight and overweight individuals (Seicnan et al., 2008). In a recent study by Pamidi et al. (2012) was assessed whether the presence of OSA affects glucose metabolism in young, lean individuals who are otherwise healthy and free of cardiometabolic disease. Men with OSA had lower insulin sensitivity (estimated by the Matsuda index) and higher total insulin

secretion than the controls. These findings provide evidence to support the hypothesis that OSA may be associated with early changes in the natural history of type 2 diabetes even in the absence of obesity.

The idea has been put forward that nocturnal breathing disorders comprise glucose metabolism either due to repeated oxygen desaturation or due to disturbed sleep per se. The present study suggests that indeed disturbed sleep itself deteriorates glucose metabolism, as non-obese RLS patients devoid of any nocturnal breathing problem showed impaired glucose tolerance to the same extent as OSA patients. The positive correlation between quantitative measures of sleep interruptions (apnea-arousal-index in OSA and PLMS-arousal-index in RLS) and 2h-plasma glucose levels in the OGTT indicate repeated arousals as a possible common mechanism of impaired glucose tolerance in both sleep disorders.

This idea is in line with the report of Tasali et al. (2008b), who induced impaired glucose tolerance in healthy volunteers by disturbing sleep by means of acoustical stimulation for three consecutive nights. This procedure did not alter the total amount of sleep, suggesting a specific effect of repeated arousals. Our results support this idea, because patients with primary insomnia and normal glucose tolerance had similar total sleep times compared to OSA and RLS patients, but lacked the repeated arousals induced by apneas or PLMS. Repeated arousals could affect glucose metabolism by altering sleep structure, in particular by preventing SWS. This is suggested by a correlation between SWS and insulin sensitivity in the study of Tasali et al. (2008b), where SWS was reduced by nearly 90%. Stamatakis and Punjabi (2010) fragmented sleep across all sleep stages for two nights using auditory and mechanical stimuli. Sleep fragmentation resulted in an increase in stage 1 sleep and a decrease in slow wave and in rapid eye movement sleep by preserved sleep duration. Following two nights of sleep fragmentation, insulin sensitivity and glucose effectiveness were significantly decreased. Interestingly, a recent study of Gonnissen et al. (2013) examined the effect of sleep fragmentation in healthy young men. Sleep fragmentation resulted in slightly reduced REM sleep and preserved SWS without changes in total sleep time. A single night of mildly fragmented sleep induced a shift in insulin concentrations, from being lower in the morning and higher in the afternoon.

Because we restricted polysomnographic recordings to the patient groups, the present study does not help to directly answer the question whether sleep duration or other quantitative aspects of night sleep, independently of arousing stimuli during sleep, affect glucose metabolism. Indirectly, similar sleep durations of 5.5 hours in all our patient groups, including primary insomnia patients who showed no impairment in glucose tolerance, suggests that

only more prominent sleep reduction might have a direct negative effect on carbohydrate metabolism. One example would be sleep curtailment to four hours of sleep for some days (Spiegel et al., 1999), which impaired glucose metabolism even in healthy people.

RLS is frequently found in patients with diabetes, which so far has mainly been explained by the fact that diabetes-induced polyneuropathy predisposes to RLS (Merlino et al., 2007). In line with this argument, Bosco et al. (2009) found an increased incidence of small fiber neuropathy (SFN) in RLS patients with impaired glucose tolerance. Because we did not perform skin biopsies, we cannot judge the role of SNF in our sample. However, Merlino et colleagues (2007) on the basis of multivariate analysis suggested that neuropathy only partially explains the increased prevalence of RLS in diabetics. Lim et al. (2012) postulated that abnormal sensory perception in patients with idiopathic RLS may result from impairment of central somatosensory processing rather than small fiber neuropathy. The present study for the first time suggests that not only diabetes might predispose to RLS through SNF or other mechanisms, but that in turn, RLS might be a causative factor in the development of diabetes by compromising sleep continuity due to repeated arousals.

The HPA axis study is the first one to compare the dynamic regulation of the HPA system in various sleep disorders. Compared to healthy controls, neither patients with obstructive sleep apnea, nor patients with restless legs syndrome or primary insomnia showed abnormalities in the ACTH or cortisol responses to CRH after HPA system suppression by dexamethasone. Also prior to the CRH challenge, there was no difference between groups, apart from ACTH levels which were slightly lower in RLS compared to the other samples.

These results suggest that in patients with common sleep disorders, who are carefully selected not to suffer from an affective or other psychiatric disorder, HPA system function is essentially normal.

The present findings in RLS patients are quite in line with the literature. Neither Wetter et al. (2002), Garcia-Borreguero et al. (2004), nor Hornyak et al. (2008) found abnormalities in HPA system regulation in these patients. Wetter measured cortisol plasma levels every 20 minutes for 24 hours in 10 male never medicated RLS patients with mild to moderate symptoms, Garcia-Borreguero measured plasma cortisol levels at 11 am and 11 pm in 12 patients with idiopathic RLS and matched healthy controls. No difference in feedback inhibition has been reported by Hornyak after a low dose of hydrocortisone in the evening in ten untreated patients with idiopathic RLS. Schilling et al. (2010) reported increased cortisol levels in nighttime urine. However, these results do not indicate whether this increase

observed is due to a decrease in feedback inhibition of the HPA system. Interestingly, the PLMS index and PLMS-arousal index were slightly higher in our patient's sample; sleep efficiency, a sleep parameter indicating disturbed sleep, was lower in Schilling's sample. Therefore disturbed sleep from other reasons might influence cortisol levels.

The isolated slight decrease in ACTH levels after dexamethasone suppression in RLS in the present study is probably either a finding by chance likely due to the small standard deviation observed (SD 0.2) or without major biological significance, because normal baseline cortisol levels and normal hormonal responses to CRH point to an overall normal HPA system function.

Results obtained from studies in sleep disordered breathing are quite inconsistent. Some studies reported enhanced cortisol secretion (Bratel et al., 1999) (Lanfranco et al., 2003) (Vgontzas et al., 2007). In other studies alterations in HPA system activity (Entzian et al., 1996) (Dadoun et al., 2007) were not found. Noteworthy, several of these studies were limited in that cortisol was measured at a single time point, they do not measure potential clinically important HPA system changes. Furthermore, in the majority of these studies the psychological profile, including emotional distress, anxiety, and/or depression, frequent comorbidities in OSA, were not assessed formally.

There are two studies using a CRH stimulation test in sleep apneics. In one study, ACTH responsiveness to CRH stimulation was even higher in obese subjects without OSA compared with obese OSA patients and lean controls (Vgontzas et al., 2007). In previous study, Lanfranco et al. (2004) evaluated the ACTH and cortisol response to CRH in sleep apnea patients compare with healthy obese control group and healthy non obese control group. He found the ACTH response to CRH significantly higher in sleep apnea and obese compare to non obese and even higher in sleep apnea than in obese. In both studies, basal ACTH and cortisol levels were similar in all groups and also the cortisol response to CRH was not significantly different. Exaggerated ACTH response to provocative stimuli has been already shown by several studies in obesity (Pascquali et al., 1996) (Arvat et al., 2000). ACTH hyper-responsiveness to provocative stimulation not coupled to the enhancement of the cortisol response was reported by some studies too (Tassone et al., 2002). The absence of cortisol hypersecretion in association to the enhanced ACTH response to CRH could reflect reduced adrenal sensitivity to ACTH, even more pronounced in OSA then in simple obesity (Lanfranco et al., 2004). Another explanation would be that this finding could reflect a disturbance in the control of proopiomelanocortin and related peptides such as melanocortins

and agouti-related peptides, involved in regulation of feeding behavior, insulin levels and body weight (Cone, 1999).

Only one study has been published focusing on feedback sensitivity of the HPA system in OSA patients (Carneiro et al., 2008). In this study, after administration of a low dose of dexamethasone smaller cortisol suppression has been detected in OSA patients compared to healthy controls. In our study we cannot confirm this difference in negative feedback sensitivity. The difference of our findings from that report may be a result of methodological differences. Carneiro and coworkers included OSA patients suffering from morbid obesity (BMI: 46.9 ± 2.0) while we studied less obese OSA patients (BMI: 32.9 ± 5.4). Furthermore, as negative feedback sensitivity was assessed differently, the suppressive effect of dexamethasone was measured at a different time points.

Primary insomnia is thought to be a disorder of hyperarousal. It has been shown that chronic primary insomnia is associated with increased evening and nocturnal cortisol levels (Rodenbeck et al., 2002) (Vgontzas et al., 2001a) reflected by altered parameters of the cortisol rhythm. Evening cortisol levels have been shown to be associated with the number of nocturnal awakenings during the following sleep period in chronic insomnia patients as well as in healthy controls. In contrary, our findings are in line with the study of Riemann et al. (2002) who also reported the lack of increased cortisol secretion in patients with primary insomnia. Moreover, a study in insomniacs in constant routine protocol condition (in an isolated, temperature- and light-controlled, sound-attenuated sleep laboratory) did not reveal any statistically significant difference in cortisol levels (Varkevisser et al., 2005).

Indeed, insomniacs are characterized by worrying about sleep, especially during the period of sleep (Harvey, 2000). Since the test was performed during daytime, absence of worrying about sleep, conditioned arousal to the bedroom and anticipation anxiety might prevent the cortisol hypersecretion.

Our results suggest that negative feedback sensitivity is not affected by repeated arousals during night neither in OSA, RLS nor in insomnia patients. This is in line with the result obtained by Späth-Schwalbe et al. (1991) who reported a rapid habituation of the HPA system to repeated arousals during night.

We could not confirm our hypothesis that disturbed sleep from different reasons leads to increased activity in the HPA system. In contrast, we could confirm the impaired glucose tolerance in obstructive sleep apnea and restless legs syndrome, two sleep disorders

characterized by frequent repeated arousals from sleep, but not in insomnia. There are several physiological mechanisms that might link the disturbed sleep with impaired glucose sensitivity.

Repeated arousals could have a direct effect on glucose metabolism by the resulting in activation of the sympathetic nervous system. Sympathetic output has been shown to be negatively affected by sleep disturbances. In a study of restricted sleep to 5.5 hours, a significant increase was observed in 24-hour epinephrine, as well as a nighttime increase in norepinephrine (Nedeltcheva et al., 2009). Reductions in sleep quality without changes in duration also have demonstrable effects on sympathetic output (Stamatakis and Punjabi, 2010).

Increases in heart rate and blood pressure are typical of both obstructive apneas and periodic leg movements, and sympathetic nervous system activation has been shown in both OSA and RLS patients (Narkiewicz and Somers, 2003) (Walter and Rye, 2009). In above mentioned Stamatakis and Punjabi´s study (2010) sleep fragmentation caused alterations in sympathovagal balance, with a shift toward increased sympathetic nervous system activity during sleep and wakefulness. Moreover, Tasali et al. (2011) found that the change in insulin sensitivity after CPAP was positively correlated with the magnitude of decrease in norepinephrine levels, the primary peripheral neurotransmitter of sympathetic activity, after controlling for BMI in young obese women with polycystic ovary syndrome. Importantly, the decrease in 24-h norepinephrine levels occurred in all subjects with greater reductions being observed with increasing hours of CPAP use.

Sympathetic activation raises levels of circulating free fatty acids due to the stimulation of lipolysis promoting insulin resistance by direct sympathetic innervations of the adipose tissue (Ip et al., 2002). Catecholamines also increase intracellular cAMP thereby inhibiting leptin mRNA expression and secretion (Slieker et al., 1996). Inhibition of leptin signaling will subsequently lead to an increase in feeding behavior, which will itself stimulate leptin production and feedback in an inhibitory manner to reduce catecholamine secretion. If sympathetic activation remains abnormally elevated, the hunger drive would remain high as well and lead to an increase in individual susceptibility to weight gain and obesity (Broussard and Brady, 2010).

Insufficient sleep leads to a general enhancement of markers for inflammatory activity. Cytokines, such as tumor necrosis factor alpha (TNF alpha) or interleukin 1 are clearly involved in sleep wake regulation. Sleep fragmentation as well as episodic hypoxia contribute

to release of proinflammatory cytokines, including tumor necrosis factor alpha and interleukin-6 (IL-6) (Kruger, 2008). These cytokines are linked with diabetes. Visceral adipose cells produce significant amounts of proinflammatory cytokines. TNF alpha may lead to insulin resistance, hyperglycemia, and compensatory hyperinsulinemia (Ruan et al., 2002). Evidence supporting a key role for TNF alpha in obesity-related insulin resistance came from studies showing that deletion of TNF alpha or TNF alpha receptors resulted in significantly improved insulin sensitivity in both diet-induced obese mice and leptin-deficient ob/ob mice (Uysal et al., 1997) IL-6 may induce gluconeogenesis in liver, hyperglycemia and compensatory hyperinsulinemia (Pradhan et al., 2001). However the effect of IL-6 on hepatic glucose production is still under debate. One may speculate that persistent systemic increases of IL-6 in states of chronic inflammation such as obesity and type 2 diabetes may trigger insulin resistance, whereas transient increases may contribute to normal glucose homeostasis (Rabe et al., 2008). TNF alpha and IL-6 modulate insulin resistance through several distinct mechanisms, including c-Jun N-terminal kinase 1-mediated serine phosphorylation of insulin receptor substrate-1 (IRS-1), IκB kinase-mediated nuclear factor-κB activation, and induction of suppressor of cytokine signaling-3 (SOCS-3) (Tigl and Hotamisligil 2006).

Conclusions

To conclude, the present study confirmed increased rates of impaired glucose tolerance in patients with OSA and for the first time suggests that not only diabetes might predispose to RLS through SNF or other mechanisms, but that in turn, RLS might be a causative factor in the development of diabetes by compromising sleep continuity due to repeated arousals.

This is very fist study using the DEX-CRH-test in various sleep disorders suggests that disturbed sleep per se has no major negative impact on the negative feedback inhibition of the HPA system. Furthermore, abnormalities in HPA system regulation in OSA, RLS and insomnia patients reported earlier seem to be independent of negative feedback regulation processes of the HPA system.

Reported high prevalence of diabetes in chronic sleep disorders calls for further extended investigations, because sleep disorders are highly prevalent and might represent an important preventive target to avoid metabolic disorders. Moreover, the present results further strengthen the idea that disturbed sleep in general and chronic sleep disorders in particular might significantly contribute to the steady increase in diabetes prevalence worldwide.

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