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Plasma levels of neuropeptides and metabolic hormones, and sleepiness in obstructive sleep apnea

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KEYWORDS
OSA;
Sleep apnea;

Summary
Background: Obstructive sleep apnea (OSA) is related to obesity and metabolic disorders. The main clinical symptoms are excessive daytime sleepiness (EDS) and snoring. However, not all

Abbreviation: AHI, Apnea–hypopnea index; BMI, Body mass index; CO_2, Carbon dioxide; CPAP, Continuous positive airway pressure; CRP, C-reactive protein; CSF, Cerebrospinal fluid; EDS, Excessive daytime sleepiness; EDTA, Ethylenediamine tetra-acetic acid; EIA, Enzyme immunoassay; ESS, Epworth Sleepiness Scale; OSA, Obstructive sleep apnea; RIA, Radio immunoassay; SaO_2, Oxygen saturation; SD, Standard deviation; VIP, Vasoactive intestinal peptide.

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EDS;
Metabolism

patients with OSA manifest EDS. Hypocretin-1, neuropeptide Y, leptin, ghrelin and adiponectin are implicated in both metabolic and sleep regulation, two conditions affected by OSA. We hypothesized that levels of these peptides may be related to EDS in OSA patients.
Methods: We included 132 patients with EDS, as defined by an Epworth Sleepiness Scale (ESS) score $\geq$13 (mean $\pm$ SD, 15.7 $\pm$ 2.3) and 132 patients without EDS as defined by an ESS score $\leq$9 (6.5 $\pm$ 1.9). All patients had an apnea–hypopnea index (AHI) $\geq$ 20 h^{-1}. Both groups were matched for gender (males; 83.3% vs. 85.6%), age (50.15 $\pm$ 11.2 yrs vs. 50.7 $\pm$ 9.9 yrs), body mass index (BMI) (31.8 $\pm$ 5.6 kg m^{-2} vs. 32.1 $\pm$ 4.8 kg m^{-2}), and apnea–hypopnea index (AHI) (45.5 $\pm$ 19.1 h^{-1} vs. 43 $\pm$ 19.2 h^{-1}).
Results: OSA patients with EDS showed significantly higher plasma hypocretin-1 levels ($p < 0.001$) and lower plasma ghrelin levels ($p < 0.001$) than OSA patients without EDS. There were no statistically significant differences in neuropeptide Y ($p = 0.08$), leptin ($p = 0.07$) and adiponectin ($p = 0.72$) between the two groups. In the multiple linear regression model ESS score was associated with plasma levels of hypocretin-1, ghrelin and total sleep time.
Conclusion: Our study shows that EDS in patients with OSA is associated with increased circulating hypocretin-1 and decreased circulating ghrelin levels, two peptides involved in the regulation of body weight, energy balance, sympathetic tone and sleep–wake cycle. This relationship is independent of AHI and obesity (two key phenotypic features of OSA).

Introduction

Obstructive sleep apnea (OSA), a disease that affects about 4% of the general population, is a chronic condition characterized by repetitive collapse of the upper airway during sleep leading to significant hypoxemia, sleep fragmentation, and excessive daytime sleepiness (EDS).[1,2] The existing definition of EDS in the International Classification of Sleep Disorders[3] is based on the behavior of unintentionally falling asleep and difficulty maintaining alertness. EDS is considered an important health problem, leading to road accidents, psychosocial morbidity and poor quality of life.[4] EDS has been associated with cardiac dysfunction. Patients with EDS manifest significantly lower baroreflex sensitivity and significantly higher low-to-high frequency spectral power ratios of heart rate variability during the various stages of nocturnal sleep.[5] Although EDS is one of the main symptoms of sleep apnea, for unclear reasons not all patients with OSA complain of EDS. In fact, about 15% of patients with OSA do not report EDS.[6,7] The pathogenesis of EDS in OSA patients appears to be related to underlying intermittent hypoxia and disrupted sleep. However, EDS is also related to metabolic and sympathetic activities. In a previous study, we have shown that EDS in OSA is associated with insulin resistance, independently of obesity.[8]

Hypocretin-1 (also known as orexin-A) is a neuropeptide that influences arousal and the sleep–wake cycle, cardiovascular function, temperature, metabolic rate and locomotor activity.[9,10] Neuropeptide Y is a neurotransmitter that stimulates appetite and is involved in the regulation of sympathetic activity, body weight, and energy balance.[11,12] Leptin is a protein produced in adipose tissue that interacts with receptors in the hypothalamus to inhibit eating and control body weight and fat distribution. Ghrelin is a stomach-derived peptide that has been related to the regulation of body weight through stimulation of the appetite. Finally, adiponectin, a hormone that is closely related to metabolism, is secreted by adipocytes and may have both anti-atherogenic and anti-inflammatory properties.[13]

The aim of this study was to address determinants of sleepiness in patients with OSA. It evaluated plasma levels of neuropeptides (hypocretin-1 and neuropeptide Y) and metabolic hormones (ghrelin, leptin and adiponectin) in OSA patients and their relationship with EDS in two cohorts of patients, one with OSA and another either with or without EDS, matched for age, gender, apnea–hypopnea index (AHI) and body mass index (BMI). These markers are related to energy metabolism, arousal and sympathetic activity, pathways that are altered in OSA and that may be associated with manifestations of EDS in OSA patients.

Materials and methods

Patients

We included 132 patients with EDS and 132 patients without EDS. All patients had an AHI $\geq$ 20 h^{-1}. Participants were recruited from subjects who were seen at the sleep units of four teaching hospitals in Spain. Both groups of patients were matched for gender, age, BMI and AHI. Exclusion criteria were the presence of chronic obstructive pulmonary disease, chronic inflammatory intestinal diseases, liver cirrhosis, diabetes mellitus, depression, thyroid dysfunction, rheumatoid arthritis, chronic renal failure, psychiatric disorders, malignant tumors (particularly gastric tumors), gastric surgery and/or the use of drugs that could affect sleep. None of the patients were being treated with continuous positive airway pressure (CPAP) at the time they were enrolled in the study.

Daytime sleepiness was assessed using the Spanish version of the Epworth Sleepiness Scale (ESS).[14] ESS scores $\geq$13 were considered indicative of EDS, while ESS scores $\leq$9 were considered to represent an absence of EDS. Patients with an ESS score higher than 9 and lower than 13 were excluded from the study, because such ESS scores do not allow for an accurate delineation of EDS status.

All patients included in the study provided written consent after being fully informed of the goals, methods and potential risks of the study. The Ethics Committee of the participating institutions approved this project.

Measurements

OSA diagnoses were established by overnight polysomnography, which included recordings of oronasal airflow, thoracoabdominal movements, electrocardiography, electroculography, electroencephalography, Chin electromyography, and arterial oxygen saturation measurements. Apnea was defined as the absence of airflow for more than 10 s. Hypopnea was defined as an airflow reduction greater than 50% that lasted for more than 10 s and resulted in arousal or oxygen desaturation greater than 4%.[15] Oronasal flow was measured with both a nasal pressure transducer and an oronasal thermistor. Polysomnography screening was done according to international guidelines. AHI was defined as the number of apneas plus hypopneas per hour of sleep.

Due to the known variations in hormonal levels within the sleep/wake cycle[16] blood samples were collected in all patients immediately after morning awakening. Venous blood samples were obtained from an antecubital vein using a collecting tube with ethylenediamine tetraacetic acid (EDTA). Blood samples were centrifuged, and the plasma fraction was immediately separated into aliquots and stored at −80 °C until analysis. Blood in EDTA tubes and aliquots of plasma were transported in dry ice from participating hospitals to the Arnau de Vilanova Hospital, and stored at −80 °C pending centralized analysis.

Plasma hypocretin-1 levels were measured using a previously validated[17] Enzyme immunoassay (EIA) system designed for measuring hypocretin-1 in plasma (Phoenix Pharmaceuticals, California, USA). The assay sensitivity for hypocretin-1 was 0.22 ng/ml with intra- and inter-assay coefficients of variation of <5% and <14%, respectively. Specificity of the hypocretin-1 assay was 100% with no cross-reactivity (0%) with orexin-A 16−33, agouti-related protein 83−132-amide, neuropeptide Y, α-melanocyte stimulating hormone or leptin. Plasma neuropeptide Y levels were measured using an EIA system (Phoenix Pharmaceuticals, California, USA). The assay sensitivity for neuropeptide Y was 0.09 ng/ml. Specificity of the assay for neuropeptide Y was 100% with no cross-reactivity (0%) with peptide YY, pancreatic polypeptide, vasoactive intestinal peptide (VIP), insulin, amylin or somatostatin. Ghrelin, leptin and adiponectin plasma levels were measured using commercially available ELISA kits (Phoenix Pharmaceuticals Inc., Burlingame, CA; DRG Instruments GmbH, Germany; and Mediadiagnost, Reutlingen, Germany, respectively). Intra- and inter-assay coefficients of variation for ghrelin were less than 5% and less than 9%, for leptin they were 6.43% and 10.1%, and for adiponectin were 3.37% and 6.05%, respectively. Measurements were always done in duplicate, and mean values were used for analysis. Glucose and triglyceride concentrations were determined by standard enzymatic methods using a Hitachi 917 biochemical analyzer (Roche Diagnostics, Indianapolis, USA). Plasma C-reactive protein (CRP) was measured using a chemoluminescent immunometric assay (Inmunolite 2000 High Sensitivity CRP).

Statistical analysis

Results are shown as means ± standard deviations (SD). Differences between groups were assessed by the Mann−Whitney non-parametric test for quantitative variables and the Fisher's exact test for dichotomous categorical variables. Correlations between variables of interest were assessed using the non-parametric Spearman test.

A multivariate linear regression model was used to assess the association of hypocretin-1, neuropeptide Y, ghrelin, leptin and adiponectin plasma levels with ESS values, adjusting by potential confounding factors (both known confounding factors as well as variables differently distributed in both study groups). Only statistically significant variables or confounding factors were kept in the model. All data analyses were performed using the SPSS (version 16) statistical software. *P* values lower than 0.05 were considered statistically significant.

Results

Table 1 shows pertinent anthropometric and clinical data for the two study groups. OSA was severe in both groups, as demonstrated by their high AHI scores. Percentage of time with $SaO_2 < 90\%$ and F1 sleep was lower in patients with excessive daytime somnolence, and total sleep time was higher in this group.

Plasma hypocretin-1 levels were higher in patients with EDS than in those without EDS (2.52 ± 0.25 ng ml^{-1} vs. 1.64 ± 0.17 ng ml^{-1}, $p < 0.001$). Plasma neuropeptide Y levels show a tendency (non-significant) to be lower in patients with EDS (0.91 ± 0.07 ng ml^{-1} vs. 0.97 ± 0.06 ng ml^{-1}, $p = 0.087$) (Fig. 1). Plasma ghrelin levels were lower in patients with EDS than in those without EDS (6.34 ± 3.52 ng ml^{-1} vs. 8.94 ± 5.74 ng ml^{-1}; $p < 0.001$; Fig. 2). Plasma leptin levels were similar in patients with and without EDS (11.45 ± 10.6 ng ml^{-1} vs. 10.12 ± 13.27 ng ml^{-1}; $p = 0.071$), and this was also true for plasma adiponectin levels (5.42 ± 2.98 μg ml^{-1} vs. 5.47 ± 2.78 μg ml^{-1}; $p = 0.728$; Fig. 2).

We assessed the association of ESS, BMI and AHI with neuropeptides and metabolic hormones and found that ESS score was related to hypocretin-1 and ghrelin, and BMI was related to leptin and ghrelin (Table 2).

The adjusted multivariate linear regression model used to explain ESS score showed a statistically significant relationship with ghrelin and hypocretin-1 levels, together with the total sleep time. ESS score was not associated with AHI and BMI.

Discussion

These results show that, compared to OSA patients without EDS, plasma levels of hypocretin-1 were elevated in OSA patients with EDS, whereas plasma levels of ghrelin were reduced. These relationships were independent of obesity

Table 1 Anthropometric and clinical characteristics (mean ± SD) of OSA patients with and without EDS.

	OSAS patients (n = 264)		p-value
	With EDS (n = 132)	Without EDS (n = 132)	
Sex, m [n (%)]	110 (83.3)	113 (85.6)	0.61
Age, years	50.15 (11.27)	50.72 (9.96)	0.797
BMI*, Kg/m^2	31.85 (5.68)	32.18 (4.84)	0.191
Epworth Scale	15.77 (2.32)	6.55 (1.97)	*by design*
AHI*, (events/h^{-1}	45.53 (19.11)	43.05 (19.23)	0.251
TST*, (min)	351.26 (50.53)	314.83 (72.65)	**<0.001**
% Time with SaO_2 <90%	11.95 (21.6)	15.02 (21.05)	**0.03**
F1 sleep, (%) of sleep	6.26 (9.76)	10.92 (8.65)	**<0.001**
F2 sleep, (%) of sleep	64.95 (13.5)	66.19 (9.71)	0.789
F3 + F4 sleep, (%) of sleep	14.25 (10.8)	11 (7.84)	0.08
REM sleep, (%) of sleep	15.37 (9.91)	14.33 (6.59)	0.55
Glucose, (mg/dl)	101.74 (18.07)	102.3 (16.96)	0.854
Triglycerides$^+$, (mg/dl)	134 (98.75)	125.5 (98.75)	0.521
SBP*, (mm Hg)	131.72 (16.88)	131.08 (15.06)	0.434
DBP*, (mm Hg)	82 (14.05)	82.33 (10)	0.542
Nocturnal heart rate, (bpm)	65.18 (11.07)	64.79 (9.2)	0.743
Cigarette smokers, [n (%)]	40 (15.06)	30 (11.7)	0.257
CRP*, (mg/l)	3.64 (4.84)	3.62 (4.01)	0.473

*EDS; Excessive Daytime Sleepiness, BMI; Body Mass Index, AHI; Apnea–hypopnea index, TST; Total sleep time, SBP; Systolic blood pressure, DBP; Diastolic blood pressure, CRP; C-reactive protein. $^+$Median (IQR).
The statistically significant p values are denoted by bold.

and the number of apneas during sleep (two key phenotypic features of OSA). No differences were found in the plasma levels of neuropeptide Y, leptin and adiponectin between these two groups. The present study has the largest number of patients of any to address this issue so far, and the two groups included in the study were well characterized for the presence or absence of daytime sleepiness. These results could indicate a relationship between EDS in patients with OSA and plasma levels of hypocretin-1 and ghrelin, two peptides that participate in metabolic and sleep regulation.

The origin and function of hypocretin-1 in plasma is unknown, but it is postulated that plasma hypocretin-1 may originate from leaks in the blood–brain barrier and from peripheral synthesis.[18,19] Some authors have reported lower plasma hypocretin-1 levels in patients with OSA than controls.[20–22] Nevertheless, others reported otherwise.[23,24] These discrepant findings could be related to the different populations studied and to methodological issues with hypocretin-1 assays. These studies also analyzed the correlation of certain clinical variables associated with OSA and plasma hypocretin-1 levels. Nishijima et al.[21] showed significant negative correlations with ESS. Nevertheless others authors did not find a significant correlation with ESS score.[20,23] We found a statistically significant linear correlation between hypocretin-1 and ESS score (Table 2). Hypocretin-1 is a neuropeptide that influences the sleep–wake cycle, arousal regulation and the maintenance of the alert state.[9] It could be hypothesized that the increased plasma hypocretin-1 observed in OSA patients with EDS could indicate a mechanism that facilitate wakefulness and counteracts the effects of sleepiness.

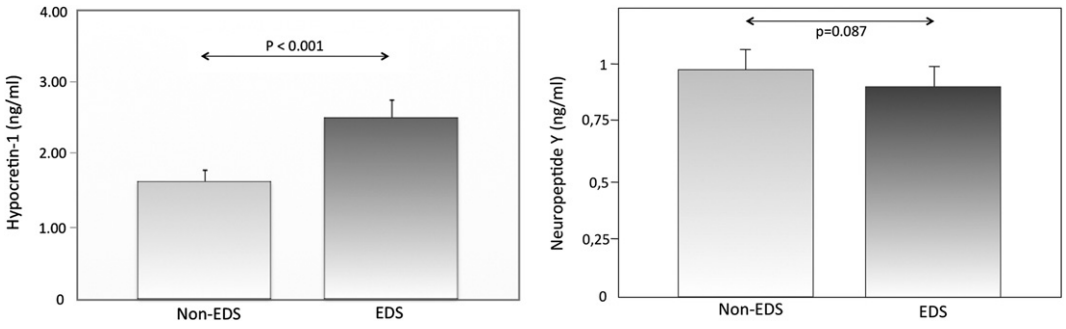

Figure 1 Plasma levels of neuropeptides in OSA patients with and without EDS (mean ± C.I. 95%).

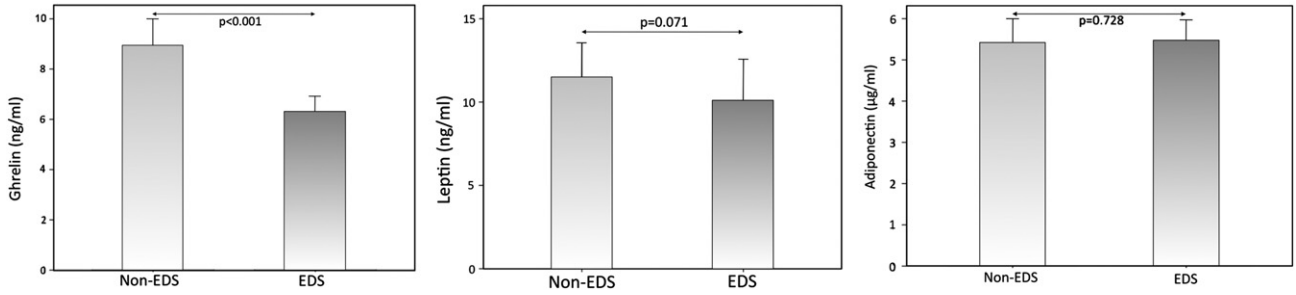

Figure 2 Plasma levels of metabolic hormones in OSA patients with and without EDS (mean ± C.I. 95%).

Patients with sleep apnea and without EDS would not be able to activate these mechanisms and therefore OSA patients would be less susceptible to the effects of sleep apnea and would not manifest EDS.

Previous studies have analyzed neuropeptide Y plasma levels in OSA patients. Barceló et al.[25] described increased levels of neuropeptide Y in OSA patients compared with control subjects. Although plasma neuropeptide Y values were lower in our patients with EDS than in patients without EDS, the differences were small and did not achieve statistical significance (Fig. 2). Plasma neuropeptide Y levels did not appear to be correlated with clinical factors, such as BMI, AHI and ESS.

In the present study we also analyzed the relationship between EDS and plasma levels of three metabolic hormones: ghrelin, leptin and adiponectin. We found that plasma ghrelin levels were lower in OSA patients with EDS than in patients without EDS. Previous studies have shown that plasma ghrelin levels are higher in patients with OSA compared to controls.[26] Plasma ghrelin levels could be modulated by, or conversely, modulate EDS in the context of OSA. Indeed, synthesis of ghrelin hormone is affected by sleep duration, as shown by Taheri et al., such that short sleep duration was associated with elevated plasma ghrelin levels.[27] In our study, as might be expected, patients without EDS, who had higher plasma ghrelin levels than patients with EDS, were also those with shorter sleep duration, assessed by total sleep time. After adjustment for confounding variables, the relationship between ESS score and plasma ghrelin levels remained statistically significant. There was no difference between OSA patients with and without EDS in plasma levels of leptin. This hormone has been positively correlated with BMI, suggesting the presence of leptin resistance in the context of obesity.[28] As expected, we found a significant positive correlation between BMI and plasma leptin levels in our study (Table 2). We did not find any significant differences in plasma leptin levels between OSA patients with and without EDS. We also did not find any differences in plasma adiponectin levels between these two groups.

In the present study ESS score was not associated with AHI and BMI. The possible correlation between daytime sleepiness and AHI is unclear.[1,29–31] Previous studies have also indicated an association between BMI and EDS, but we did not find this association in our study. Bixler et al.[32] described an association between EDS and BMI in the general population with a BMI between 18 and 69 kg m^{-2}. Nevertheless, our study population of OSA patients may be different from the general population. Also, in Bixler et al. the presence of EDS was established based on a moderate or severe rating on either of two questions. Nevertheless, in our study we performed a more accurate daytime sleepiness characterization using the Spanish validated version of the Epworth Sleepiness Scale (ESS).[14] In the present study, we also found a statistically significant relationship between ghrelin and hypocretin-1 levels with the total

Table 2 Linear correlation values for the analysis of neuropeptides/metabolic hormones, and clinical and anthropometric variables.

	BMI	ESS	AHI
Hypocretin-1	$r = 0.03$	$r = 0.3$	$r = 0.07$
	$p = 0.69$	$\mathbf{p < 0.0001}$	$p = 0.23$
Neuropeptide Y	$r = 0.01$	$r = -0.08$	$r = 0.06$
	$p = 0.92$	$p = 0.18$	$p = 0.29$
Ghrelin	$r = 0.155$	$r = -0.236$	$r = 0.083$
	$\mathbf{p = 0.01}$	$\mathbf{p < 0.001}$	$p = 0.17$
Leptin	$r = 0.368$	$r = 0.03$	$r = 0.001$
	$\mathbf{p < 0.001}$	$p = 0.73$	$p = 0.81$
Adiponectin	$r = 0.1$	$r = 0.03$	$r = 0.02$
	$p = 0.11$	$p = 0.93$	$p = 0.82$

*BMI; Body mass index, ESS; Epworth sleep scale, AHI; Apnea–hypopnea index.
The statistically significant p values are denoted by bold.

sleep time. Nevertheless, we can observe the existence of an association but we cannot indicate causality.

The present study has several strengths: its multicentric design, close matching of study subjects for gender, age, BMI and AHI, and large sample size. In addition, the exclusion of patients with ESS scores in the range where substantial overlap occurs allowed for better demarcation of those patients with EDS and those without EDS. However, our study has several limitations that deserve comment: First, sleepiness was assessed using subjective methods, rather than using a multiple sleep latency test. As mentioned, we did not include patients in the study with ESS scores between 10 and 12, in order to improve the discriminatory value of the Epworth score. Second, in the present study, the associations between metabolic hormones and neuropeptides were analyzed from a single morning sample, rather than from multiple samples within the circadian cycle. Third, we did not include the treatment effect. An interventional study would enable better discrimination of the strength of the associations described herein and would enable confirmation of their validity. Indeed, if improvements in sleepiness were predicted by changes in any of these plasma markers or combinations thereof, the intrinsic roles and clinical value of such assays would be greatly enhanced.

Conclusions

Our study shows that EDS in patients with OSA is associated with increased circulating hypocretin-1 and decreased circulating ghrelin levels, two peptides involved in the regulation of body weight, energy balance, sympathetic tone and sleep—wake cycle. This relationship is independent of AHI and obesity (two key phenotypic features of OSA).

Author contributions

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Drafting of the article: Sánchez de la Torre M., Barbé F.

Critical review of the article for important intellectual content: Barceló A., Pierola J., Esquinas C., Martinez M., de Lecea L., Gozal D., Barbé F.

Recruitment of patients: Sánchez de la Torre M., Barceló A., Pierola J., de la Peña M., Durán J., Capote F., Masa J.F., Cao G., Marin J.M., Barbé F.

Statistical analyses: Sánchez de la Torre M., Esquinas C., Martinez M., Barbé F.

Funding procurement: Sánchez de la Torre M., Barceló A., de la Peña M., Durán J., Capote F., Masa J.F., Marin J.M., Barbé F.

Administrative, technical, or logistic support: Sánchez de la Torre M., Barceló A., Pierola J., de la Peña M., Durán J., Capote F., Masa J.F., Marin J.M., Cao G., Barbé F.

Data collection: Sánchez de la Torre M., Barceló A., de la Peña M., Durán J., Capote F., Masa J.F., Marin J.M., Barbé F.

Conflict of interest disclosures

None declared.

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