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CPAP Treatment Contributes to Some Neuropeptide and Weight Change in Patients with Obstructive Sleep Apnea

Obstrüktif Uyku Apneli Hastalarda CPAP Tedavisi Bazı Nöropeptid ve Kilo Değişimine Katkı Sağlar

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ÖZET

Amaç: Bu çalışmada obstrüktif uyku apnesi sendromu (OSAS)'na bağlı obezitenin ortaya çıkışında hipotalamik beslenmeyi düzenleyici nöropeptitler olan Nöropeptid Y (NPY), Orexin, pro-opiomelanokortin (POMC) ve leptin seviyeleri ile PAP tedavisi ile gözlenen kilo değişimi arasında bir ilişki olup olmadığının araştırılması amaçlandı.
Gereç ve Yöntem: Çalışmaya Göğüs Hastalıkları uyku laboratuvarında OSAS tanısı alan ve PAP tedavisi planlanan 18-65 yaş arası 38 gönüllü erkek hasta dahil edildi. Hastalarda OSAS tanısı aldıktan sonra ve PAP tedavisinden 6 ay sonra kan örneği alındı. ELİZA yöntemi ile nöropeptid seviyeleri belirlendi.
Bulgular: Otuz sekiz erkek hastanın yaş ortalaması 47.82±1.64'dü. OSAS tanılı hastalarda 6 aylık PAP tedavisi sonunda Leptin, NPY, Orexin ve POMC düzeyleri vücut kitle indeksi (VKİ)'nden bağımsız olarak düşüktü ve istatistiksel olarak anlamlıydı (p>0,001).
Sonuç: Apnelerin ortadan kaldırılması, oksijenasyonun sağlanması, PAP tedavisi ile uyku parçalanmasının düzeltilmesi, hipoksik etkinin ve buna bağlı olarak inflamasyonun büyük ölçüde azaltılması ile metabolik stabilitenin sağlandığını düşünmekteyiz. Hastaların PAP cihazlarının gece boyunca kesintisiz kullanımının sağlanması ve teşvik edilmesi tedavinin etkinliğini ön plana çıkaracaktır. Ayrıca cihazı kullanırken diyet ve egzersiz programlarının verilmesi fazla kilolu hastalarda BKİ'nin düşürülmesinde etkili olacaktır.

Anahtar Kelimeler: CPAP, leptin, NPY, POMC, orexin, uyku apnesi

ABSTRACT

Aim: It was aimed to investigate whether there is a relationship between hypothalamic nutrition regulatory neuropeptides Neuropeptide Y (NPY), Orexin, pro-opiomelanocortin (POMC) and leptin levels in the emergence of obesity associated with OSAS and the weight change observed with PAP treatment.
Materials and Methods: Thirty-eight male volunteer patients aged 18-65 who were diagnosed with OSAS and planned for PAP treatment in the sleep laboratory of Chest Diseases were included in the study. Blood samples were taken from the patients after the diagnosis of OSAS and 6 months after PAP treatment. Neuropeptide levels were determined by ELISA method.
Results: Thirty-eight male patients the mean age was 47.82±1.64 years. Leptin, NPY, Orexin and POMC levels were lower and statistically significant in OSAS patients after 6 months of PAP treatment, independent of body mass index (BMI) (p>0.001).
Conclusion: We think that metabolic stability is achieved by eliminating apneas, providing oxygenation, correcting sleep fragmentation with PAP therapy, reducing the hypoxic effect and accordingly inflammation to a large extent. As a result, ensuring and encouraging the uninterrupted use of PAP devices by patients throughout the night will highlight the effectiveness of the treatment. In addition, giving diet and exercise programs while using the device will be effective in lowering BMIs for overweight patients.

Key words: CPAP, leptin, NPY, POMC, orexin, sleep apnea

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INTRODUCTION

The international classification of sleep disorders divides sleep-related breathing disorders into three groups: obstructive sleep apnea syndrome (OSAS), central sleep apnea syndrome, and sleep-related hypoventilation/hypoxemic syndromes. The most common of three groups is OSAS. OSAS is defined as a disease characterized by recurrent episodes of complete (apnea) or partial (hypopnea) upper airway obstruction during sleep and often a decrease in blood oxygen saturation (1). Polysomnography (PSG), the gold standard diagnostic method, is used for the diagnosis of OSAS and the selection of positive airway pressure therapy (PAP) (2,3). Although anatomical condition, alcohol use, hypercholesterolemia, type 2 diabetes mellitus and hypertension are risk factors in OSAS, obesity is one of the important risk factors for OSAS. Obesity is defined as body mass index (BMI)≥30, while BMI ≥25.0 indicates that the person is overweight (4). Although one of the most important factors affecting obesity is eating habits, there are many mechanisms that regulate food intake in the body. Neuropeptides that regulate food intake include neuropeptide Y (NPY), orexin, pro-opiomelanocortin (POMC), and leptin. Disturbances in these mechanisms increase the susceptibility to obesity, and cardiovascular diseases and sleep problems occur as a result of obesity.

NPY is a neuropeptide produced in the central nervous system and is involved in the regulation of many neuroendocrine functions, including nutrition, central autonomic functions, daily circadian rhythm, regulation of sleep-wake cycle, regulation of blood pressure, learning, stress responses, sexual and motor behaviors (5). In the fasting state, the release of Orexin increases. Orexigenic neurons are stimulated when blood glucose is low and the stomach is emptied, increasing food intake (6). POMC is the forerunner of αMSH (α-Melanocyte stimulating hormone), the main regulator of energy balance (7). The main role of leptin in the body is to regulate food intake and energy metabolism and to prevent the development of obesity with a negative feedback effect on the brain. In the fasting state, leptin level drops rapidly and food intake is increased. Genetic absence of leptin or its receptor is associated with hyperphagia and obesity syndromes (8).

In the light of this information, it was aimed to investigate whether there is a relationship between hypothalamic nutrition regulatory neuropeptides NPY, Orexin, POMC and leptin levels in the emergence of obesity associated with OSAS and the weight change observed with PAP treatment.

MATERIALS AND METHODS

The study was conducted prospectively in Chest Diseases Sleep Laboratory between 2019-2020. Thirty-eight patients who were diagnosed with OSAS and started PAP treatment were included in the study.

Study design

Demographic characteristics of the patients (height, weight, BMI, additional disease history, alcohol use) were recorded in the study file.

PSG Test and PAP Treatment

Epworth sleepiness scale was used to evaluate excessive daytime sleepiness and 10 points and above were evaluated as pathological. PSG test was applied to all patients in order to confirm the diagnosis of the patients. This test included oro-nasal airflow recording (thermistor or oro-nasal cannula), belt to record thorax and abdomen movement (measurement of stretch), 2-channel ECG (electrocardiogram), chin-EMG (submental electromyogram), and leg-EMG (leg electromyogram), right and left EOG (electrooculogram), 6 channel EEG (electroencephalogram F4-M1, C4-M1, O2-M1), transcutaneous oxygen saturation probe (pulse oximeter), snoring sensor (microphone) recordings. Patients were classified according to the apnea/hypopnea index (AHI) diagnostic criteria after PSG, with AHI <5 normal, AHI 5-15 mild, 15-30 moderate, 30 and above severe OSAS. 5 ml blood samples were taken from the patients to determine the neuropeptide plasma levels before PAP treatment. Then, for PAP treatment, the patients were hospitalized for one more night in the sleep laboratory in order to determine the appropriate device and pressure with PSG. Patients were treated with PAP for 6 months (using device at least 4 hours every night) in the presence of appropriate treatment parameters, and 5 ml blood samples were taken again to determine the changes in neuropeptide levels after the treatment.

Pre and post-treatment central and peripheral neuropeptides levels were determined using the ELISA study method.

Statistical Analysis

Jamovi 1.2.27 statistics program was used in the analyses. The distributions of the data were analyzed with the Kolmogorov Smirnov test. Wilcoxon signed-rank test was used to analyze pre- and post-treatment measurements of dependent variables for non-normally distributed parameters, and paired t-test for normally distributed data. Results were expressed as Median, 1st Quarter and 3rd Quartile with Z values. Normally distributed data were expressed as mean ± standard error of mean (SEM). P value of 0.05 was considered statistically significant.

RESULTS

38 male patients were included in the study and the mean age was 47.82±1.64 years. Demographic characteristics and anthropometric measurements of the patients are shown in Table 1. AHI and Epworth values were different before and

Table 1. Demographic and anthropometric characteristics of patients and statistical analysis results.

Parameters	Mean±SEM
Age (Years)	47.82±1.64
AHI Pre (Event/Hour)*	49.41± 4.64
AHI Post (Event/Hour)	6.68±0.97
Epworth Sleep Scale Pre*	10.95±1.57
Epworth Sleep Scale Post	5.18±0.65
BMI Pre (kg/m^2)	30.95±0.81
BMI Post (kg/m^2)	31.41±0.87
Waist Circumference-Pre (cm)	108.82±2.01
Waist Circumference-Post (cm)	109.45±2.17
Neck Circumference-Pre (cm)	43.30±0.59
Neck Circumference-Post (cm)	43.27±0.59
PAP device using (day)	178.55±1.77

Anthropometric and demographic characteristics of patients (n=38). *p <0.001. Other parameters p>0.05. The effect of the change in normal distribution parameters was looked at by paired test. AHI: Apnea hypopnea index, BMI: Body mass index, PAP: Positive airway pressure

after treatment as expected. While the mean AHI value was 49.41±4.64 before PAP treatment, this value was 6.68±0.97 after. This change in AHI value was found to be statistically significant (p<0.001). While the mean ESS value was 10.95±1.57 before PAP treatment, this value was 5.18±0.65 after (p <0.001). BMI, waist and neck circumference were not to be statistically significant before and after treatment (p>0.05).

The values of central and peripheral neuropeptides included in the study before and after PAP treatment are shown in Table 2. The changes in NPY, orexin, PMOC and leptin before and after PAP treatment were found to be statistically significant (respectively p=0.001, p=0.019, p=0.01, p=0.001 respectively).

DISCUSSION

In this study, Leptin, NPY, Orexin, and POMC levels (p<0.001) were decreased in OSAS patients who were effectively treated with approximately 180 days of device use, independent of BMI.

NPY is a neurotransmitter that interacts with leptin in the regulation of sympathetic activation, body weight, and energy balance. In the hypoxia model created in rats, it was shown that NPY levels increased by 56% in the carotid body and 99% in the anterior pituitary gland (9). Although there are not many studies between continuous positive airway pressure (CPAP) treatment and NPY, a study conducted in 2004 showed that NPY levels were reduced in patients with OSAS, and leptin levels only in nonobese patients, independent of obesity (10). In our study, it was found that NPY levels decreased approximately 40% after treatment, but there was no significant difference in BMI levels (respectively p=0.001 and p>0.05).

Orexin and its receptors are concentrated in the central nervous system, and orexin levels increase in fasting (11). In an animal study, arousal stimulation has been shown to increase orexin levels (12). Igarashi et. al. in their study in 2003, they reported that orexin may be involved in arousal mechanisms, and that orexin levels and Epworth sleepiness scale decreased in 12 of 30 OSAS patients with 3-month CPAP use (11). In another study, it was reported that orexin levels were lower in patients with untreated OSAS. However, it was shown that orexin levels were lower in 14 OSAS patients who received treatment for 1 year (13). In our study, the orexin levels of treated OSAS patients were found to be significantly decreased and were found to be compatible with the literature (p=0,019).

Activated by leptin, POMC provides an appetite-reducing stimulus. To our knowledge, our study is the first to demonstrate that POMC levels are regulated by PAP therapy. The literature on POMC regulation in human focuses mostly on experimental studies. POMC protein and exspression levels has been shown to increase in wild-type rats exposed to intermittent hypoxia (14), but not in the leptin-deficient rat (15). Also, by intermittent hypoxia, mRNA levels of POMC and CART up-regulated in human neuronal cells via GATA transcription factors (16). Moreover, mice lacking leptin signaling in POMC neurons have been shown to have altered expression of hypothalamic neuropeptides, and mildly obese,

Table 2. Statistical analysis results and changes in neuropeptides before and after PAP treatment

Neuropeptides	Median (1st Quartile-3rd Quartile)	Z/P Values
Leptin-Pre	98.35 (74.08-135.08)	-3.328 / 0.001
Leptin-Post	18.15 (14.10-23.23)	
NPY-Pre	62.65 (50.88-81.33)	3.279 / 0.001
NPY-Post	25.15 (21.80-45.28)	
Orexin-Pre	76.65 (63.20-108.30)	-2.354 / 0.019
Orexin-Post	14.65 (10.93-19.58)	
POMC-Pre	53.10 (39.53-80.45)	-3.295 / 0.01
POMC-Post	20.75 (14.98-30.38)	

The effect of the change in non-normal distribution parameters was looked at with the Wilcoxon sign-rank test. n=38. POMC: Leptin (pg/mL); NPY: Neuropeptid Y, Orexin, Proopiomelanokortin (ng/L).

hyperleptinemic (17). POMC level decreased significantly by about 55% after PAP treatment in our study. This may indicate the direct effect of treatment of intermittent hypoxia due to sleep apnea.

The main role of leptin is to regulate food intake and energy metabolism and to prevent the development of obesity with a negative feedback effect on the brain. It also plays a role in the regulation of sexual development, reproduction, sympathetic nervous system activation and gastrointestinal system (GIS) functions. Leptin achieves its metabolic effects through its specific receptors located in the central nervous system and peripheral tissues (18). In a meta-analysis study conducted in 2014, it was emphasized that leptin levels decreased without a simultaneous weight loss, especially after CPAP treatment (19,20). After 1 month of CPAP use, leptin concentrations decreased significantly, and after 6 months of CPAP treatment, a decrease in visceral adipose tissue can be observed even if there is no loss of BMI (21,22). Similarly, leptin concentrations decreased significantly in our study. The decrease in leptin level shown may be the control of leptin secretion by the effect of PAP treatment on sympathetic activation (23,24). Hemodynamic changes such as increase in lung volume and decrease in thoracic pressure that occur with treatment may affect cardiac sympathetic function and affect leptin secretion. However, the mechanisms are still unclear. In addition, tissue or arterial oxygenation may contribute to leptin regulation (24). It has been shown that leptin production is increased under hypoxic conditions for PAZ6 cultured cells (25). However, acute intermittent hypoxia can also cause an increase in circulating leptin levels. Because leptin acts as a proinflammatory adipokine, it can increase the chronic inflammatory state (26). In our study, it can be thought that the cause of the decrease in leptin levels without a change in BMI is that the chronic inflammatory state due to OSA disrupts leptin regulation by creating leptin resistance or causing leptin excess and has a systemic effect. The effect on sympathetic activation may be the reason for the decrease in plasma leptin levels due to the improvement of night sleep, increase in oxygenation, and decrease in thoracic pressure after treatment.

Our study has several potential limitations that open to comment. First, we started our study with 60 patients with OSA, but the patients either did not get their devices or gave up treatment. Secondly, our patients had a BMI of 30 or above. The number of admissions to the clinic for potential non-obese OSA patients was not enough, and should have been included in the study to the extent of the lab facilities. So, it would allow us to distinguish between an obesity-related change. We didn't make any measurements of the central nervous system except for measuring plasma levels. Finally, although parameters such as fasting blood glucose, hemogram, and blood lipids were checked in the first routine examination of the patients, they were not repeated in the second measurements.

Pathological respiratory events occurring during the night with OSA cause intermittent hypoxia. However, inflammation caused by hypoxia affects the release of central and peripheral neuropeptides by various mechanisms. PAP treatment may mediate the regulation of neuropeptides. It also causes sleep fragmentation of apneas that occur during the night. In this case, the metabolism is seriously affected. We think that metabolic stability is achieved by eliminating apneas, providing oxygenation, correcting sleep fragmentation with PAP treatment, reducing the hypoxic effect and accordingly inflammation to a large extent. For this reason, ensuring and encouraging the uninterrupted use of PAP devices throughout the night will highlight the effectiveness of the treatment. In addition, we believe that giving diet and exercise programs while using the device will be effective in lowering BMIs for overweight patients.

Etik Kurul: The studies reported herein were approved by Institutional Review Board (Confirmation number: 2018/1418).

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