Inflammation and sleep disordered breathing in children: a state-of-the-art review.

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Sleep disordered breathing (SDB) represents a spectrum of breathing disorders, ranging from snoring to obstructive sleep apnea syndrome (OSAS), that disrupt nocturnal respiration and sleep architecture. OSAS is a common disorder in children, with a prevalence of 2-3%. It is associated with neurobehavioral, cognitive, and cardiovascular morbidities. In children, adenotonsillectomy is the first choice for treatment and is reserved for moderate to severe OSAS, as defined by an overnight polysomnography. In adults, OSAS is the result of mechanical dysfunction of the upper airway, manifesting as severity-dependent nasal, oropharyngeal, and systemic inflammation that decrease after continuous positive airway pressure therapy. Inflammatory changes have been reported in upper airway samples from children with OSAS, and systemic inflammation, as indicated by high-sensitivity C-reactive protein (hsCRP) levels, has been shown to decrease in children with OSAS after adenotonsillectomy. Anti-inflammatory treatments for children with mild OSAS are associated with major improvements in symptoms, polysomnographic respiratory values, and radiologic measures of adenoid size. Inflammation is correlated to some extent with OSAS-related neurocognitive morbidity, but the role of inflammatory markers in the diagnosis and management of OSAS, and the role of anti-inflammatory treatments, remains to be clarified.

This review examines the role of inflammation in the pathophysiology of sleep-disordered breathing in pediatric patients and the potential therapeutic implications. (c) 2008 Wiley-Liss, Inc.

Regulation of oxidative stress and cardioprotection in diabetes mellitus.

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Department of Internal Medicine III, Osaka Medical College. Analysis of the Framingham data has shown that the risk of heart failure is increased substantially among diabetic patients, while persons with the metabolic syndrome have an increased risk of both atherosclerosis and diabetes mellitus. Sleep apnea may be related to the metabolic syndrome and systemic inflammation through hypoxia, which might also cause the cardiac remodeling by increased oxidative stress. On the other hand, the renin-angiotensin system is activated in diabetes, and local angiotensin II production may lead to oxidative damage via the angiotensin II type 1 receptor. Basic and clinical data indicate that angiotensin II receptor blockers have the potential to preserve left ventricular function and prevent cardiac remodeling that is exaggerated by oxidative stress in patients with diabetes. Thus, alleviation of oxidative stress might be one possible strategy in the treatment of diabetic patients associated with sleep apnea.
Intermittent hypoxia and activation of inflammatory molecular pathways in OSAS.

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Obstructive sleep apnoea syndrome (OSAS) represents a highly prevalent disease and is recognized as a risk factor for the development of various cardiovascular disorders. The pathogenesis of cardiovascular complications in OSAS is not completely understood, but the unique form of hypoxia with repetitive short cycles of desaturation followed by rapid reoxygenation termed intermittent hypoxia (IH) is likely to play a significant role. There is increasing evidence that IH leads to a preferential activation of inflammatory over adaptive pathways. This promotes activation of various inflammatory cells, particularly lymphocytes and monocytes, with the downstream consequence of expression of pro-inflammatory cytokines, chemokines and adhesion molecules that may contribute to endothelial dysfunction. This review provides a critical analysis of the current evidence of inflammatory mechanisms initiated by IH that may contribute to the cardiovascular pathogenesis in OSAS.

Correlation of 8-isoprostane, interleukin-6 and cardiac functions with clinical score in childhood obstructive sleep apnoea.

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OBJECTIVE: Adeno-tonsillar hypertrophy is the commonest cause of childhood obstructive sleep apnoea (OSA). Our aim of the study is to correlate the severity of OSA with levels of 8-isoprostane and interleukin-6 (IL-6) and with cardiac diastolic dysfunctions. METHODS: Forty children with adenoidal hypertrophy and 20 control children were recruited. The OSA clinical score was evaluated and IL-6 and 8-isoprostane were measured in exhaled breath condensate. The cardiac functions were evaluated by conventional and tissue Doppler echocardiography (TDE).

RESULTS: Higher concentrations of isoprostane-8 and IL-6 were found in group with clinical score >40 (58.595 +/- 2.86 pg/mL and 38 +/- 1.77 pg/mL, respectively) than in control group (34.9 +/- 1.5 pg/mL and 7.02 +/- 0.3 pg/mL, respectively) [p < 0.0001*]. There was positive correlation between level of isoprostane-8 and IL-6 and value of clinical score [p < 0.0001*] and also with the degree of the cardiac dysfunction in those children.

CONCLUSION: The severity of OSA as indicated by
clinical score was positively correlated with degree of
elevation of 8-Isoprostane and IL-6 in breath condensate
of children with OSA and also with degree of cardiac
dysfunction. Echocardiography and tissue Doppler
modality are advised to examine these children.


Sleep-disordered breathing and
systemic inflammation in overweight
children and adolescents.

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OBJECTIVE: To assess if the severity of sleep-disordered
breathing (SDB) and mainly intermittent hypoxia is
associated with increased peripheral leukocytes in
overweight children and adolescents, controlling for
adiposity and obesity-related metabolic abnormalities.

METHODS: Consecutive subjects were recruited at a
pediatric obesity clinic. All subjects underwent
Polysomnography and a fasting blood sample.

RESULTS: In total, 95 subjects were included (<age>
=11.1±2.6, 43 boys, body mass index, <BMI z-
score>=2.3±0.5, 29 subjects were overweight and 66
obese). Total white blood cell count increased significantly
by worsening of intermittent hypoxia. Total white blood
cell count was correlated with the maximal degree of
desaturation, independent of puberty, HOMA and HDL-
cholesterol. Neutrophil levels were associated with the
degree of desaturation, while controlling for puberty and
HOMA.

CONCLUSION: This study supports the hypothesis of
an independent interaction between intermittent hypoxia
and nocturnal desaturation during sleep, and increased
white blood cell and neutrophil levels in overweight and
obese children and adolescents. This finding may contribute to the mechanisms linking SDB with increased cardiovascular morbidity.


Airway inflammation in obstructive
sleep apnea: is leptin the missing link?

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BACKGROUND: Local and systemic inflammation is
implicated in the pathophysiology of Obstructive Sleep
Apnea (OSA). Exhaled breath condensate (EBC) is a non-
invasive sampling method for the lower airways. However, it is important to consider the potential effect of the systemic origin whereas systemic inflammation is
significantly elevated. This prospective study was designed
to investigate whether airway inflammation is
significantly related to plasma leptin levels in OSA patients.
Simultaneously, it was designed to investigate whether
inflammatory variables predict parameters expressing
disease severity and finally whether smoking habit affect
the above measurements.

PATIENTS & METHODS: About 45 OSA patients
(mean AHI 40±25, 28 smokers) and 25 healthy controls
(AHI<5, 15 smokers) were studied and underwent
overnight diagnostic polysomnography. We measured
pH, 8-isoprostane, TNF-alpha and IL-6 in EBC and leptin
in plasma. Plausible associations between leptin and
inflammatory parameters were analyzed after adjustment
for proper variables. Similar associations between
inflammatory variables and parameters of disease severity
were also performed.

RESULTS: An increased level of leptin and respective
increase of inflammatory variables was found. No
significant association was observed between parameters
of EBC and plasma leptin levels. The observed airway inflammation seemed to be
independent of smoking habit with limited association
with disease severity.
Association between serum neopterin, obesity and daytime sleepiness in patients with obstructive sleep apnea.

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OBJECTIVE: Obesity and obstructive sleep apnea (OSA) and systemic inflammation may interact through biochemical pathways. Neopterin (NP) is a monocyte/macrophage activation marker produced by macrophages in response to interferon-gamma secreted by activated T-lymphocytes. This study examines the association between NP, obesity and OSA.

PATIENTS AND METHODS: The study included 22 newly diagnosed OSA (+) patients and 18 OSA (-) patients. Subjects with history of coronary artery disease, transplant patients, history of alcohol and drug abuse, history of HIV and any other significant medical illnesses such as active infections, autoimmune disease, malignancy, liver disease, pulmonary disease (COPD, asthma,...), neuromuscular disease, patients on immunomodulating therapy or HMG-CoA reductase inhibitors were excluded.

RESULTS: There were no significant differences in age, body mass index (BMI), and smoking habits of the OSA (+) patients and OSA (-) patients. Serum NP levels did not show any significant difference between the OSA (+) patients and OSA (-) patients, however, NP levels were positively correlated with BMI (r=0.320, p=0.044). There was no significant correlation between NP and any of the polysomnographic parameters. The result of stepwise regression analyses (r(2)=0.320, p<0.001) showed that high serum NP levels (p=0.004) and apnea-hypopnea index (AHI) were a risk factor for elevated Epworth sleepiness score, independent of BMI.

CONCLUSION: We suggest that serum NP levels correlate with BMI. There was a significant relationship between serum NP levels and excessive daytime sleepiness in OSA patients.

Relationship between inflammation and cognitive function in obstructive sleep apnea.

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OBJECTIVES: Obstructive sleep apnea (OSA) can have adverse effects on cognitive functioning, mood, and cardiovascular functioning. OSA brings with it disturbances in sleep architecture, oxygenation, sympathetic nervous system function, and inflammatory processes. It is not clear which of these mechanisms is linked to the decrease in cognitive functioning. This study examined the effect of inflammatory parameters on cognitive dysfunction.

MATERIALS AND METHODS: Thirty-nine patients with untreated sleep apnea were evaluated by polysomnography and completed a battery of neuropsychological tests. After the first night of evaluation in the sleep laboratory, blood samples were taken for analysis of interleukin 6, tumor necrosis factor-alpha (TNF-alpha), and soluble TNF receptor 1 (sTNF-R1).

RESULTS: sTNF-R1 significantly correlated with cognitive dysfunction. In hierarchical linear regression analysis, measures of obstructive sleep apnea severity explained 5.5% of the variance in cognitive dysfunction (n.s.). After including sTNF-R1, percentage of variance explained by the full model increased more than threefold to 19.6% (F = 2.84, df = 3, 36, p = 0.05). Only sTNF-R1 had a significant individual relationship with cognitive dysfunction (beta = 0.376 t = 2.48, p = 0.02).

CONCLUSIONS: sTNF-R1 as a marker of chronic inflammation may be associated with diminished neuropsychological functioning in patients with OSA.

Predictors of fatigue in obstructive sleep apnea.

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OBJECTIVE: The objective of this study was to determine potential inflammatory predictors of fatigue in obstructive sleep apnea (OSA).

MATERIALS AND METHODS: Fifty-six women and men untreated OSA patients had their sleep monitored with polysomnography. Fatigue was assessed by the Multidimensional Fatigue Symptom Inventory-Short Form. Depressed mood was assessed by the Center for Epidemiologic Studies-Depression Scale. Blood was drawn to assess circulating levels of Interleukin-6 (IL-6) and soluble tumor necrosis factor receptor I (sTNF-RI). Age, gender, body mass index (BMI), blood pressure, OSA severity, depressed mood, and inflammatory biomarkers were entered into a hierarchical multiple linear regression analysis predicting self-reported fatigue.

RESULTS: Approximately 42% of the patients reported significant amounts of fatigue. Higher BMI (p = 0.014), greater depressed mood (p = 0.004), and higher sTNF-RI levels (p = 0.033) were independent predictors of fatigue in the final model (full model R² = .571; p = .003). Age, gender, blood pressure and apnea severity were unrelated to fatigue.

CONCLUSION: The findings suggest that in addition to depressed mood, fatigue in OSA may be associated with increased body weight and elevated levels of the proinflammatory cytokine receptor sTNF-RI. The findings support a linkage between the widely reported fatigue in OSA and a sleep-related component of inflammation.


CPAP decreases plasma levels of soluble tumour necrosis factor-alpha receptor 1 in obstructive sleep apnoea.

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There is increasing evidence that inflammation plays an important role in the development of cardiovascular complications in patients with obstructive sleep apnoea (OSA). No previous works have studied levels of soluble tumour necrosis factor-alpha receptor (sTNFR)-1 in patients with OSA. The aims of the present study were to examine serum levels of sTNFR-1 and the effect of nasal continuous positive airway pressure (CPAP) in patients with OSA. A prospective, randomised, placebo-controlled crossover study was performed. In total, 30 consecutive newly diagnosed OSA patients (apnoea/ hypopnoea index 43.8+/-27.0 events x h(-1)) and 15 healthy obese patients were selected. Urinary levels of norepinephrine and epinephrine, as well as plasma sTNFR-1, tumour necrosis factor (TNF)-alpha, interleukin (IL)-6 and leukotriene (LT)B(4) levels were obtained at baseline and after 3 months of CPAP or sham CPAP. Nocturnal urinary levels of norepinephrine, epinephrine and sTNFR-1 (1,053+/-269 versus 820+/-166 pg x mL(-1)) were significantly higher in OSA patients. There were no significant differences in plasma levels of IL-6, LTB(4), or TNF-alpha between the two study groups. There were no significant differences in blood pressure, urinary catecholamine levels, or plasma sTNFR-1, TNF-alpha levels after both treatment modalities. However, after 3 months of effective CPAP usage, sTNFR-1 levels were significantly reduced (1,053+/-269 versus 899+/-254 pg x mL(-1)). Obstructive sleep apnoea patients have higher levels of soluble tumour necrosis factor-alpha receptor 1 than individuals without OSA; soluble tumour necrosis factor-alpha receptor 1 levels are lowered by continuous positive airway pressure therapy. These findings further corroborate a potential role of inflammation in the natural history of obstructive sleep apnoea.


Increased low-grade inflammation and plasminogen-activator inhibitor-1 level in nondippers with sleep apnea syndrome.

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OBJECTIVE: Patients with sleep apnea syndrome have an increased risk of cardiovascular events and frequently show a nondipper pattern (blunted nocturnal decline <10%) of systolic blood pressure. We investigated
neurohumoral activation and risk factors in relation to nocturnal blood pressure dipping pattern and sleep apnea syndrome.

METHODS: We conducted sleep polysomnography and ambulatory blood pressure monitoring and measured high-sensitivity C-reactive protein, tissue-type plasminogen activator inhibitor-1, and neurohumoral factors in 121 outpatients with suspected sleep apnea syndrome who were classified into four groups on the basis of the presence of the absence of dipping/nondipping and sleep apnea syndrome.

RESULTS: Nondippers with sleep apnea syndrome had higher high-sensitivity C-reactive protein (overall P<0.001), plasminogen activator inhibitor-1 (overall P=0.004), and aldosterone levels (overall P=0.010) than any of the other three groups. After adjustment for significant covariates such as age, sex, body mass index, waist circumference, smoking, alcohol drinking, aspirin use, presence of diabetes, and insulin, nondippers with sleep apnea syndrome still had a higher high-sensitivity C-reactive protein level than nondippers without sleep apnea syndrome (geometric mean: 1.47 vs. 0.37 mg/l, P = 0.001). In multiple linear regression analysis controlling for confounding factors related with sleep apnea syndrome, high-sensitivity C-reactive protein was significantly correlated with 3% oxygen desaturation index (P=0.047). Plasminogen activator inhibitor-1 level was also highest in the nondippers with sleep apnea syndrome but not independent of obesity. Plasminogen activator inhibitor-1 level correlated with insulin (r=0.32, P=0.002) and high-sensitivity C-reactive protein levels (r=0.26, P=0.005).

CONCLUSION: Nondipper status was associated with an increased high-sensitivity C-reactive protein level in patients who also had sleep apnea syndrome but not in those who did not. High-sensitivity C-reactive protein level was closely affected by the desaturation level. Plasminogen activator inhibitor-1 level is also increased in nondippers with sleep apnea syndrome and is related to insulin and high-sensitivity C-reactive protein levels.

Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea.

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BACKGROUND: Indirect evidence implicates endothelial dysfunction in the pathogenesis of vascular diseases associated with obstructive sleep apnea (OSA). We investigated directly whether dysfunction and inflammation occur in vivo in the vascular endothelium of patients with OSA. The effects of continuous positive airway pressure (CPAP) therapy on endothelial function and repair capacity were assessed.

METHODS AND RESULTS: Thirty-two patients with newly diagnosed OSA and 15 control subjects were studied. Proteins that regulate basal endothelial nitric oxide (NO) production (endothelial NO synthase [eNOS] and phosphorylated eNOS) and inflammation (cyclooxygenase-2 and inducible NOS) and markers of oxidative stress (nitrotyrosine) were quantified by immunofluorescence in freshly harvested venous endothelial cells before and after 4 weeks of CPAP.
therapy. Vascular reactivity was measured by flow-mediated dilation. Circulating endothelial progenitor cell levels were quantified to assess endothelial repair capacity. Baseline endothelial expression of eNOS and phosphorylated eNOS was reduced by 59% and 94%, respectively, in patients with OSA compared with control subjects. Expression of both nitrotyrosine and cyclooxygenase-2 was 5-fold greater in patients with OSA than in control subjects, whereas inducible NOS expression was 56% greater. Expression of eNOS and phosphorylated eNOS significantly increased, whereas expression of nitrotyrosine, cyclooxygenase-2, and inducible NOS significantly decreased in patients who adhered to CPAP ≥ 4 hours daily. Baseline flow-mediated dilation and endothelial progenitor cell levels were lower in patients than in control subjects, and both significantly increased in patients who adhered to CPAP ≥ 4 hours daily.

CONCLUSIONS: OSA directly affects the vascular endothelium by promoting inflammation and oxidative stress while decreasing NO availability and repair capacity. Effective CPAP therapy is associated with the reversal of these alterations.


Cortistatin—functions in the central nervous system.

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Cortistatin (CST) is a neuropeptide from the somatostatin (SRIF)/urotensin (UII) family named after its predominantly cortical expression and ability to depress cortical activity, which was discovered a decade ago. In vitro assays show CST is able to bind all five cloned somatostatin receptors and shares many pharmacological and functional properties with SRIF. However, distinct from SRIF, CST has been shown to induce slow-wave sleep, reduce locomotor activity, and activate cation selective currents not responsive to somatostatin. Different lines of evidence also indicate that CST, like SRIF, is involved in learning and memory processes. CST-14 may also function as an endogenous anti-convulsant. In addition to its role in cortical synchronization, CST-14 has emerged as an important mediator of immunity and inflammation. This review will cover some of the basic properties of CST in the brain, and will discuss new data on the role of CST in cortical activity.

Sleep-Disordered Breathing, Obesity, and Airway Inflammation in Children and Adolescents

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BACKGROUND: To investigate the relationship between obstructive sleep apnea syndrome (OSAS) and exhaled nitric oxide (eNO) in overweight children and adolescents without asthma or atopy and to assess whether obesity per se is associated with increased airway inflammation.

METHODS: Consecutive overweight subjects without symptoms of asthma or allergy were recruited at a pediatric obesity clinic. A normal-weight control group without OSAS and asthma or allergy was also recruited. All subjects underwent polysomnography and two measurements of eNO (afternoon and morning after polysomnography).

RESULTS: Controlling for age, the mean (± SD) afternoon eNO concentration was significantly higher in the snoring group (14.1 ± 1.1 parts per billion [ppb]) compared with the normal-weight group (10.1 ± 0.8 ppb; p = 0.03) and with the overweight group with normal polysomnography findings (8.9 ± 0.8 ppb; p = 0.007). The afternoon eNO concentration was also different between the OSAS group (11.9 ± 1.0 ppb) and the overweight group with normal polysomnography findings.
Morning eNO values were higher in the OSAS group (12.3 ± 1.1 ppb) than in the normal weight group (9.9 ± 0.8 ppb; p = 0.047) and in the overweight control group (9.7 ± 0.7 ppb; p = 0.02). BMI z score was not significantly correlated with afternoon eNO concentration or with morning eNO concentration.

CONCLUSION: This study illustrates that both habitual snoring and OSAS are associated with increased airway inflammation in overweight children as assessed by higher eNO levels. Furthermore, it was demonstrated that childhood obesity in the absence of sleep-disordered breathing is not associated with increased airway inflammation.

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Euktoriene B4: early mediator of atherosclerosis in obstructive sleep apnoea?


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ABSTRACT: Severity of oxygen desaturation is predictive of early atherosclerosis in obstructive sleep apnoea (OSA). Leukotriene (LT)B4 is a lipid mediator involved in atherogenesis. In 40 non-obese OSA patients, free of a cardiovascular history, and 20 healthy volunteers, the following were evaluated: 1) LT4 production by polymorphonuclear leukocytes (PMNs) stimulated with A23187; and 2) the relationships between LT4 production and both OSA severity and infraclinical atherosclerosis markers. The effect of continuous positive airway pressure (CPAP) on LT4 production was also studied. An overnight sleep study was followed by first morning blood sampling. Isolated PMNs were stimulated with A23187 in order to induce LT4 production, which was measured by liquid chromatography–tandem mass spectrometry. Carotid intima-media thickness (IMT) and luminal diameter were measured in subset groups of 28 OSA patients and 11 controls. LT4 production was increased in OSA patients compared with controls. LT4 levels correlated with the mean and minimal arterial oxygen saturation (Sa,O2). LT4 production correlated with luminal diameter data in patients with a mean Sa,O2 of 94% but not with IMT. Lastly, CPAP significantly reduced LT4 production by 50%. Leukotriene B4 production is increased in obstructive sleep apnoea in relation to oxygen desaturation. Leukotriene B4 could promote early vascular remodelling in moderate-to-severe hypoxic obstructive sleep apnoea patients.

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Impairment of serum albumin antioxidant properties in obstructive sleep apnoea syndrome

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ABSTRACT: Antioxidant counteraction of oxidative stress has been poorly explored in obstructive sleep apnoea (OSA). Serum albumin is a major antioxidant agent and structural modifications induced by glucose or free radicals impair its antioxidant properties. The aim of the present study was to compare antioxidant capacities and structural changes of albumin in nonobese OSA patients and healthy volunteers. Albumin structural changes were studied by quenching of fluorescence in the presence of acrylamide. Albumin thiol and fructosamines, reflecting oxidation- and glycation-induced changes in serum albumin, respectively, were assessed. Albumin structural changes were demonstrated by a significant decrease in quenching of fluorescence in OSA patients. Oxidation, resulting in a significant decrease in thiol groups (3.7 ± 0.7 versus 2.3 ± 0.4 micro mol·g⁻¹ protein), and glycation, associated with a significant increase in fructosamines (226.6 ± 27 versus 286 ± 44.4 micro mol·L⁻¹), were found when comparing healthy volunteers with OSA patients. There was a significant relationship between both parameters and sleep apnoea severity. After continuous positive airway pressure intervention, albumin thiol groups were reduced.
reassessed in seven of the 16 OSA patients and increased significantly from $2.25\pm0.39$ to $2.79\pm0.31$ micro mol g$^{-1}$ protein. Obstructive sleep apnoea patients demonstrated a reduction in serum albumin antioxidant properties that may aggravate oxidative stress and, thus, contribute to cardiovascular and metabolic morbidities.


**Clock gene dysfunction in patients with obstructive sleep apnoea syndrome**


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**ABSTRACT:** Clock genes regulate mammalian circadian rhythms, and dysfunction of clock genes can contribute to various disorders. To investigate whether obstructive sleep apnoea syndrome (OSAS) influences clock gene function, the present authors examined Period1 (Per1) mRNA expression in vitro and in vivo. In eight healthy subjects and eight OSAS patients, plasma noradrenaline, serum interleukin (IL)-6, high-sensitivity C-reactive protein (hsCRP) and Per1 mRNA expression in peripheral whole blood were measured. Expression of Per1 mRNA in cultured cells was examined under IL-6 or noradrenaline stimulation in vitro. After noradrenaline was administrated to mice in vivo, Per1 mRNA expression in the brain was examined. The concentrations of serum IL-6, hsCRP and plasma noradrenaline were elevated in OSAS patients, but improved by continuous positive airway pressure (CPAP) therapy. Per1 mRNA expression in the peripheral blood significantly decreased at 02:00 h by CPAP in OSAS patients. Stimulation with IL-6 did not directly induce Per1 mRNA in vitro. Administration of noradrenaline induced Per1 mRNA in the cerebral cortex of mice in vivo. The current study revealed that obstructive sleep apnoea syndrome caused clock gene dysfunction, and continuous positive airway pressure helped to improve it. Sympathetic activation and elevation of the plasma noradrenaline concentration in obstructive sleep apnoea syndrome may be one of the factors involved in disorders of Period1 mRNA expression.