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Marked Decrease in Sleepiness in Patients with Sleep Apnea by Etanercept, a Tumor Necrosis Factor-α Antagonist

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The proinflammatory cytokines, TNFα and IL-6, are elevated in obstructive sleep apnea (OSA) and have been proposed as mediators of excessive daytime sleepiness in humans. We tested the effects of etanercept, a medication that neutralizes TNFα and is approved by the FDA for the treatment of rheumatoid arthritis, in eight obese male apneics. These patients participated in a pilot, placebo-controlled, double-blind study during which nighttime polysomnography, multiple sleep latency test, and fasting blood glucose and plasma levels of IL-6, C-reactive protein, insulin, and adiponectin were obtained. There was a significant and marked decrease in sleepiness by etanercept, which increased sleep latency during the multiple sleep latency test by 3.1 ± 1.0 min ($P < 0.05$) compared with placebo. Also, the number of apneas/hypopneas per hour was reduced significantly by the drug compared with placebo (52.8 ± 9.1 *vs.* 44.3 ± 10.3; adjusted difference, −8.4 ± 2.3; $P < 0.05$). Furthermore, IL-6 levels were significantly decreased after etanercept administration compared with placebo (3.8 ± 0.9 *vs.* 1.9 ± 0.4 pg/ml; adjusted difference, −1.9 ± 0.5; $P < 0.01$). However, no differences were observed in etanercept *vs.* placebo in the levels of fasting blood glucose and plasma C-reactive protein, insulin, and adiponectin. We conclude that neutralizing TNFα activity is associated with a significant reduction of objective sleepiness in obese patients with OSA. This effect, which is about 3-fold higher than the reported effects of continuous positive airway pressure on objective sleepiness in patients with OSA (0.9 *vs.* 3.1 min), suggests that proinflammatory cytokines contribute to the pathogenesis of OSA/sleepiness. (*J Clin Endocrinol Metab* 89: 4409–4413, 2004)

EXCESSIVE DAYTIME SLEEPINESS (EDS) occurs in about 5–15% of the general population, is the chief complaint of the majority of patients evaluated at sleep disorders centers, and is of major importance to public safety (1–4). Daytime sleepiness and fatigue are cardinal symptoms of obstructive sleep apnea (OSA); however, these symptoms are also associated with several medical and mental disorders, such as obesity, diabetes, and depression (5). OSA is a prevalent disorder, particularly among middle-aged, obese, men, although its existence in women as well as in lean individuals is increasingly recognized (6–9). Four percent of men and 2% of women in general population random samples meet the clinical and polysomnographic criteria for the diagnosis of sleep apnea, warranting therapeutic intervention (7–9). A much larger group, 17–24% of men and 5–9% of women, demonstrates an apnea/hypopnea index (A/HI) of more than five events per hour of sleep (7–9), a criterion which, when it is associated with symptomatology, such as excessive daytime sleepiness and/or cardiovascular problems, warrants therapeutic intervention (10). However, the majority of subjects with an A/HI of 5 or greater are asymptomatic, *i.e.* no complaint of sleepiness.

Obstructive sleep apnea is associated with considerable morbidity and mortality, whereas the current available treatments are associated with either limited efficacy and/or poor compliance (6, 11, 12). For example, a recent meta-analysis of 11 studies of the efficacy of continuous positive airway pressure, the most common mode of therapy for OSA, on sleepiness showed only a marginal effect on objective sleepiness (0.9 min) (11).

We and others have shown that the inflammatory cytokines, TNFα and IL-6, are elevated in sleep apnea and that this elevation is compounded with, but independent of, obesity (13–15). Also, these cytokines are elevated in experimentally induced sleepiness in healthy young adults after one or several nights of total sleep loss (16, 17) or partial sleep loss for 1 wk (18). There are several ways that peripheral cytokines can communicate and signal the brain to elicit central nervous system manifestation, *e.g.* sleepiness, including crossing the blood-brain barrier (19, 20) and through peripheral autonomic efferent nerves (21). Based on these findings, we have proposed that TNFα and IL-6 might play a significant role in mediating sleepiness and fatigue in disorders of EDS in humans (14–16). Furthermore, we and others have shown that there is a strong correlation between the degree of obesity and levels of TNFα and IL-6, both of which induce peripheral insulin resistance (5, 14, 15, 22–27). Thus, we have proposed that inflammation is an important mechanism involved in the multifaceted association between sleep apnea and sleepiness, and insulin resistance and visceral obesity, all of which promote atherosclerosis, cardiovascular disease, and premature death (5, 15).

Abbreviations: A/HI, Apnea/hypopnea index; EDS, excessive daytime sleepiness; MSLT, multiple sleep latency test; OSA, obstructive sleep apnea; REM, rapid eye movement.

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Etanercept (Enbrel; Immunex Corporation, Thousand Oaks, CA) is a dimeric fusion protein that binds specifically to TNF and blocks its interaction with cell surface TNFα receptors. It is an FDA-approved medication for the treatment of rheumatoid arthritis and is given in an injectable form (sc) at a dose of 25 mg twice a week (28). Etanercept intercepts the inflammatory reaction at an early step of the cascade, resulting in limitation of inflammation. The primary objective of this study was to test the effects of etanercept on sleepiness and respiratory disturbance in eight male obese apneics in a double-blind, placebo-controlled study. A secondary objective, given the association of TNFα with IL-6 and insulin resistance (22–24), was to evaluate the effect of etanercept on IL-6, insulin resistance indexes, and adiponectin, an adipocyte-derived and insulin resistance-protective hormone (29). For purely technical reasons, the presence of the drug in the plasma of the patients treated precluded accurately assaying TNFα.

Subjects and Methods

Subjects

Eight obese, middle-aged (mean age, 43.8 $\pm$ 2.8; range, 26.3–58.0 yr), male patients with sleep apnea participated in our study. Eligible participants included sleep apneics who demonstrated an A/HI of more than 20 events/h of sleep during the screening night and who had not received treatment for sleep apnea for at least the last 6 months. All patients reported daytime sleepiness, and two of them were treated for hypertension. The participants were recruited from a pool of patients who had refused any of the currently available treatments for sleep apnea. Patients with congestive heart failure, cancer, central nervous system demyelinating disorder, recurrent or active infection, or poorly controlled diabetes were excluded from the study.

At the onset of the study, the subjects had a thorough medical history and physical examination performed. In addition, a complete series of clinical laboratory tests assessing blood count and thyroid, liver, and kidney functions; a urine drug screen; and a baseline electrocardiogram were negative for abnormal findings.

Protocol

This was a pilot, placebo-controlled, double-blind study and lasted 7 wk, during which the subjects were recorded in the sleep laboratory three times: immediately before the administration of placebo (baseline), the week after the 3-wk administration of placebo (fourth week of the study), and the week after the 3-wk administration of Etanercept (seventh week of the study). We used a fixed order design *vs.* a traditional cross-over design for three reasons: 1) to control carryover effects of drug on sleep and sleepiness measures, which in a cross-over design would have required a several-week washout period and/or a significantly larger sample; 2) to minimize the possibility of change in baseline symptomatology due to a prolonged washout period; and 3) to expose the minimum of subjects to an experimental condition with untried outcomes. One limitation of the fixed order design is that it does not control for order effects.

Administration of etanercept (Enbrel)

In our study etanercept (25 mg) was administered twice a week for 3 wk. Both etanercept and placebo injections were given by the nursing staff of the General Clinical Research Center at Milton S. Hershey Medical Center, who were blind to the study design.

During these biweekly visits, the participants had their vital signs recorded and were monitored by the principal investigator and the nursing staff of the General Clinical Research Center for early signs of infection, such as fever, cough, *etc.* Only one subject complained of a sore throat and, based on clinical examination, negative findings on white blood cell count, and a consult by a rheumatologist, it was judged not to be related to the administration of etanercept.

Sleep laboratory recording

Each time in the sleep laboratory, the patients were monitored for an 8-h nocturnal polysomnographic recording (model 15 Neurodata Amplifier System, Grass-Telefactor Instrument, West Warwick, RI) for two consecutive nights according to standard methods (the first night was used for acclimatization, and the second night served as an accurate assessment of nighttime sleep as well as respiration).

Respiration was monitored throughout the night by use of a thermistor at the nose and mouth (model 1450; Sleepmate Technologies, Midlothian, VA) and thoracic strain gauges (sensor model F-RCT-A; Piezoelectric, Midlothian, VA). All-night recordings of arterial blood oxygen saturation were obtained with an oximeter (model 8800; Nonin Medical, Inc., Plymouth, MN) attached to the finger. Apnea was considered present if a breath cessation exceeded 10 sec. In addition, hypopnea was considered present when a reduction in airflow of approximately 50% was indicated at the nose or mouth and was associated with a reduction of 4% or more arterial blood oxygen saturation.

All sleep laboratory personnel having direct contact with the subjects were blind to the conditions. Furthermore, the sleep records were scored independently of any knowledge of the experimental condition according to standardized criteria (30). Sleep parameters assessed from the sleep recordings were grouped into three categories: sleep efficiency measures, amount of sleep stages, and additional rapid eye movement (REM) variables. Sleep efficiency measures included sleep induction (sleep latency), sleep maintenance (wake time after sleep onset), total wake time (sum of sleep latency and wake time after sleep onset), and percentage of sleep time (total sleep time as percentage of time in bed). The duration of sleep stages [REM, stage 1 and 2, and slow wave sleep (stages 3 and 4 combined)] was expressed as absolute minutes or as a percentage of total sleep time, which was calculated by the minutes in each stage as a percentage of total sleep time. Additionally, REM latency was calculated, which is the interval from sleep onset to the first REM period. The onset of sleep was established by the presence of any sleep stage for 1 min or longer. However, if the initial stage of sleep was stage 1, it had to be followed without any intervening wakefulness by at least 60 sec of stage 2, 3, 4, or REM.

Assessment of daytime sleepiness

During the daytime after the second night in the laboratory, the subjects' level of daytime sleepiness and alertness was evaluated using the multiple sleep latency test (MSLT) (31). Typically, the test consists of 20-min opportunities to sleep at 2-h intervals beginning at 0900 h. In our experiment we administered MSLT four times during the day (~0900, 1200, 1500, and 1700 h). The onset of sleep was established by the presence of any sleep stage for 1 min or longer. However, if the initial stage of sleep was stage 1, it had to be followed without any intervening wakefulness by at least 60 sec of stage 2, 3, 4, or REM. Also, before each nap opportunity, subjective levels of sleepiness were assessed with a seven-point question, "how sleepy do you feel right now?" and a visual analog scale that ranged from 0 (extremely sleepy) to 10 (not sleepy at all).

Single blood draws

A single morning blood draw immediately after the subjects were awakened took place during the three sleep testing periods: baseline, after the 3-wk administration of placebo, and at the end of the 3-wk administration of etanercept. Plasma levels of C-reactive protein, IL-6, fasting blood glucose, insulin, and adiponectin were assessed during each testing period, whereas, for technical reasons, TNFα was measured during baseline and placebo. C-Reactive protein was measured by ELISA. The detectable limit was 0.122 ng/ml, the intraassay variability ranged from 5.5- 6%, and the interassay variability ranged from 11.6–13.8%. Plasma TNFα and IL-6 were measured by ELISA (R&D Systems, Minneapolis, MN). The intra- and interassay coefficients of variation ranged from 5.6–6.1% and 7.5–10.4%, respectively, for TNFα and from 3.2–8.5% and 3.5–8.7% for IL-6. The lower detection limits for TNFα and IL-6 were 0.18 and 0.094 pg/ml, respectively. Plasma insulin was measured by specific RIA (Linco Research, Inc., St. Charles, MO). The intra- and interassay coefficients of variation for insulin ranged from 3.5–4.6% and 4.5–7.0%, respectively. Adiponectin was measured by RIA (Linco

Research, Inc.). The minimum detectable limit of adiponectin was 1.0 ng/ml. Interassay variability ranged from 6.9–9.25%, whereas intraassay variability ranged from 1.78–3.59%.

Analysis

The mixed effects model was applied to test, overall, whether the three pairwise differences between the three conditions of A/HI, MSLT, and hormones/cytokines were the same. This is equivalent to comparisons of the means at the three conditions, except that in the analysis the change from one condition to another was further adjusted for the value at the baseline condition. Specifically, for example, in assessing the change from placebo to treatment conditions, a patient's pretreatment placebo value was centered at its group mean, so that one can remove the influence of the pretreatment value (*e.g.* the regression to the mean effect), and the adjusted value can be informative about a differential treatment effect (32). The significance level for the overall test was chosen to be 0.05. The overall F tests for A/HI, MSLT, and IL-6 were significant, allowing individual comparisons between the placebo and baseline conditions and between the treatment and placebo conditions to be made. The former evaluated whether the administration of vehicle (placebo) had an effect on the variables assessed, and the latter assessed whether etanercept had an effect on those variables after the experience of a placebo effect. Because comparisons between baseline and placebo did not show any significant differences in all outcome variables, we present the data with a focus on treatment *vs.* placebo comparisons. The data for each condition are presented as the mean ± SE, whereas the differences are presented as the least squares mean ± SE after adjusting for the pretreatment placebo values.

Results

The average age of the eight men with OSA was 43.7 ± 3.8 yr, and their body mass index was 38.6 ± 2.6 kg/m^2. There was no change in body mass index across the three conditions (38.6 ± 2.6 at baseline, 38.4 ± 2.6 at the end of placebo, and 38.7 ± 2.2 at the end of the treatment period).

Daytime sleepiness (MSLT)

A significant increase in mean sleep latency by an average of 3.1 ± 1.0 min ($P < 0.05$) was observed between placebo and etanercept groups. Sleep latency was higher at each time point of MSLT and reached significance at 1200 and 1700 h (17.4 ± 1.5 *vs.* 11.3 ± 2.3 min and 18.2 ± 0.8 *vs.* 15.1 ± 1.8 min; Fig. 1). The differences at both time points were significant after adjusting for placebo values [adjusted difference, 5.2 ± 1.5 min ($P < 0.01$) and 5.6 ± 0.9 min ($P < 0.01$)]. Subjective sleepiness measures did not show significant differences between the placebo *vs.* treatment conditions (2.7 ± 0.3 *vs.* 2.9 ± 0.4 in the seven-point scale and 6.0 ± 0.7 *vs.* 5.9 ± 0.9 in the visual analog scale).

Nighttime sleep and respiratory data

There were no differences in any of the sleep variables among the three conditions (Table 1). The number of apneas/hypopneas per hour (A/HI) was reduced between placebo (52.8 ± 11.08) and treatment (44.3 ± 10.3) groups, and the difference was significant after adjusting for pretreatment placebo values (adjusted difference, −8.4 ± 2.3; $P < 0.05$).

IL-6, C-reactive protein, insulin, glucose, and adiponectin

No significant differences were detected among the three conditions in plasma insulin, fasting blood glucose, and adiponectin. The IL-6 level was decreased after etanercept administration compared with placebo (3.8 ± 0.9 *vs.* 1.9 ± 0.4 pg/ml; adjusted difference, −1.9 ± 0.5 pg/ml; $P < 0.01$; Fig. 2). C-Reactive protein levels were not different between placebo and treatment groups (5.8 ± 1.2 *vs.* 4.1 ± 1.3 μg/ml). Also, TNFα levels were similar in placebo and baseline groups (2.7 ± 0.6 *vs.* 2.4 ± 0.4 pg/ml; not significant).

Discussion

This study is the first to demonstrate that neutralizing TNFα activity is associated with a significant reduction of

TABLE 1. Nighttime sleep and respiratory variables at baseline, placebo, and etanercept conditions in eight obese, middle-aged men with OSA

	Baseline	Placebo	Etanercept
Sleep latency (min)	15.2 ± 3.6	13.5 ± 3.2	11.0 ± 2.6
Wake time after sleep onset (min)	80.9 ± 14.8	76.2 ± 12.2	86.0 ± 16.6
% Sleep time	80.4 ± 3.6	81.9 ± 2.6	80.9 ± 1.8
% Stage 1	18.8 ± 4.0	20.5 ± 2.8	22.9 ± 4.8
% Stage 2	66.0 ± 2.8	62.5 ± 1.8	60.0 ± 4.7
% Slow wave sleep	0.6 ± 0.3	0.9 ± 0.4	0.7 ± 0.5
% REM	15.0 ± 2.2	15.4 ± 2.0	15.6 ± 2.0
REM latency (min)	129.9 ± 10.2	100.7 ± 13.3	112.7 ± 17.4
A/HI	55.9 ± 11.6	52.8 ± 11.1	44.3 ± 10.3
Min SaO_2	68.5 ± 5.2	69.9 ± 5.4	71.6 ± 4.5

[a] Data are the mean ± SE.

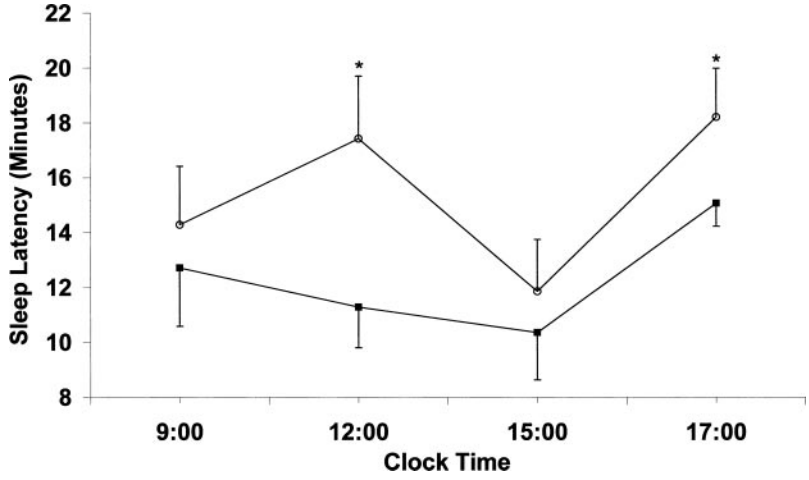

FIG. 1. Sleep latencies during daytime testing with MSLT in the placebo (■) and etanercept (○) conditions. Each *data point* represents the mean ± SE. *, $P < 0.05$, adjusted change between placebo and etanercept.

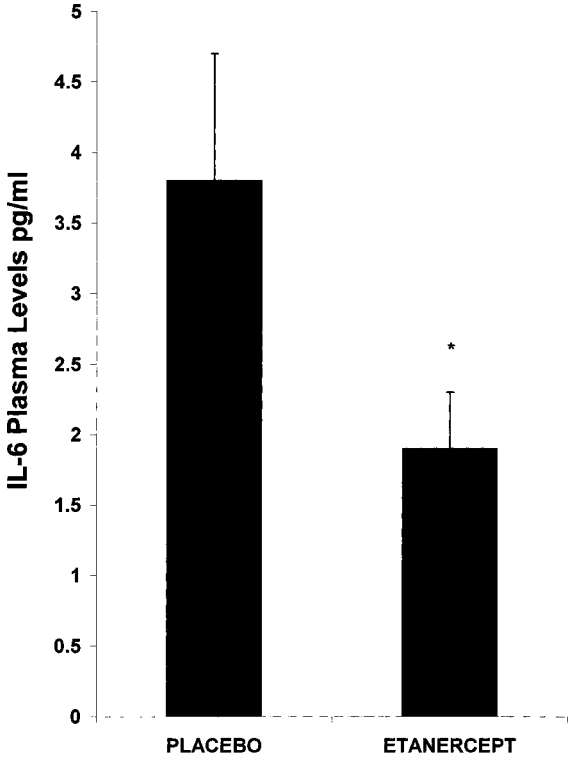

FIG. 2. Change in plasma levels of IL-6 between placebo and etanercept conditions. Data represent the mean ± SE. *, $P < 0.05$, adjusted change between placebo and etanercept.

sleepiness and sleep apnea/hypopnea in obese patients with OSA. The reduction in objective sleepiness was robust, remained significant after adjusting for placebo values, and is about 3-fold higher than the reported effects of continuous positive airway pressure, the standard of practice therapy, on objective measure of sleepiness in patients with OSA (0.9 *vs.* 3.1 min) (11). This study provides support for our proposal that proinflammatory cytokines may be mediators of excessive daytime sleepiness and fatigue in humans (14–16).

The small, but significant, improvement in A/HI observed in obese patients with severe apnea supports our previously proposed model that inflammation is part of the pathogenetic mechanisms leading to OSA (5, 15). Future studies should assess whether administration of etanercept, either for a longer period and/or in patients with mild to moderate sleep apnea, will be associated with a more marked improvement of the respiratory abnormalities.

We have previously shown that obesity, age, and diabetes/insulin resistance are stronger predictors of excessive daytime sleepiness than A/HI in patients with OSA (5). In this study the effect on sleepiness was much larger compared with the effect on respiration, suggesting that other factors besides respiratory disturbance or sleep fragmentation, such as hypercytokinemia associated with obesity and diabetes/insulin resistance, are significant independent contributors to EDS.

In this study the administration of etanercept, in addition to its TNFα receptor-blocking effects, was associated with a significant reduction of IL-6. This reduction is most likely secondary to the inactivation of TNFα, which has a stimulation effect on the secretion of IL-6 (22, 23). We have previously shown that plasma levels of IL-6 correlate with daytime sleepiness in OSA patients and in normal sleepers after sleep loss (14–16). The reduction of sleepiness associated with decreased IL-6 levels in this study provides evidence that IL-6 also is one of the mediators of EDS in humans.

Three weeks of administration of etanercept did not improve indexes of insulin resistance, including the adipocyte-derived hormone adiponectin, which appears to play a protective role against insulin resistance and atherosclerosis (29). It has been previously suggested that TNFα is a mediator of insulin resistance in animals and humans (24, 33). The lack of etanercept effect may be due to either the short duration of etanercept administration and/or the fact that other mechanisms are stronger than TNFα in the pathogenesis of insulin resistance in humans. The fact that subjective measures of sleepiness did not show an improvement may reflect this; the subjective tools used in our study are not as sensitive, *e.g.* visual analog scale, compared with the Epworth sleepiness scale, which consists of nine questions assessing sleepiness in real life situations (9), and the inherent variability of the subjective measures, which influences studies with a small sample size such as this. Finally, our method of detection and scoring hypopnea is more conservative than other criteria (34); however, it should be expected that this difference has affected the three conditions in a uniform way.

In conclusion, this is the first interventional study in which rationale was based on previous findings from observational studies (13–16) and showed that TNFα and IL-6 are mediators of sleepiness in humans and are involved in the pathogenesis of sleep apnea. The accumulating evidence on the association of sleep apnea with hypercytokinemia, visceral obesity, and insulin resistance and the results of this study suggest that interventional studies attempting to correct these abnormalities will promote understanding of the pathophysiological mechanisms of sleepiness/OSA and will lead to more effective treatments of these highly prevalent and morbid disorders.

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