Plasma Levels of Tumor Necrosis Factor α and Soluble Tumor Necrosis Factor Receptors in Patients With Narcolepsy

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Background: Narcolepsy is a disabling sleep disorder characterized by excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis. Recent studies suggest that the immune system might play a pathogenic role pointing to a possible involvement of inflammatory cytokines.

Methods: We investigated a sample of 30 patients with narcolepsy in comparison with 120 sex- and age-matched and 101 sex-, body mass index (BMI)-, and age-matched randomly selected normal controls. In these groups, plasma concentrations of tumor necrosis factor α (TNF-α) and its soluble receptors p55 and p75 (soluble TNF receptor [sTNF-R] p55 and sTNF-R p75) were measured using commercial enzyme-linked immunosorbent assays.

Results: The narcoleptic patients showed a significantly higher BMI compared with controls of the same age. Soluble TNF-R p75 levels were consistently elevated in the narcoleptic patients compared with their sex- and age-matched ($P=.001$) as well as sex-, BMI-, and age-matched counterparts ($P=.003$). Female narcoleptic patients exhibited higher sTNF-R p55 levels compared with their sex- and age-matched controls ($P=.01$), but this difference disappeared when comparing patients with sex-, BMI-, and age-matched normal controls. Tumor necrosis factor α levels did not differ significantly between groups.

Conclusion: Narcoleptic patients show increased plasma levels of sTNF-R p75, suggesting a functional alteration of the TNF-α cytokine system, further corroborating a possible pathogenic role of the immune system in this sleep disorder.

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NARCOLEPSY IS A DISabling sleep disorder that affects approximately 1 in 2000 individuals in the general US population[1] and in Europe[2] and is characterized by excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis.[3] Since the discovery of the extremely close association of narcolepsy and the human leukocyte antigen (HLA)-DR2,[4,5] it has been suggested that the immune system might play a pathogenic role because it is known that HLA haplotypes are linked to a number of autoimmune diseases.[6] In human narcoleptic patients, a drastic reduction in the number of hypocretin neurons could be observed, and also in canine and murine cases of narcolepsy, the implication of the hypocretin system is well established.[7] Because of the association of narcolepsy with HLA-DR2, it was hypothesized that the loss of these neurons might be caused by an autoimmune process.[8]

Recently, the role of cytokines, humoral mediators of the immune system, has been considered in the regulation of sleep-wake behavior, and data suggest that cytokines are involved in the generation of daytime sleepiness and fatigue.[9] In animal studies, the tumor necrosis factor α (TNF-α) system has been shown to be involved in physiological sleep regulation, and several interesting details regarding the interaction between the TNF-α system and sleep-wake behavior have been reported. For example, in mice TNF-α has been shown to affect sleep via the TNF receptors (TNF-Rs).[10,11] Also, in rabbits, in which TNF-α is also a key regulatory component of sleep, inhibition of TNF-α in the brain suppresses rabbit sleep,[12] and a complex interaction between temperature regulation, the TNF-α system, and sleep has been reported.[13]

In humans, studies have demonstrated a significant involvement of the TNF-α system in sleep-wake regulation. For example, TNF-α levels are reported to

be elevated in disorders associated with excessive daytime sleepiness, such as sleep apnea and idiopathic hypersomnia,[14] and total sleep loss has been shown to produce significant increases in plasma levels of the soluble TNF-R (sTNF-R) p55.[15] Because sTNF-Rs are a component of normal human cerebrospinal fluid,[16,17] it is possible that TNF-α and TNF-Rs are involved in the central regulation of sleep-wake behavior.

Okun et al[18] reported significantly higher TNF-α levels in narcoleptic patients compared with controls. Another study, however, could not confirm these results.[19] One methodical problem of these studies is that they did not control for age and body mass index (BMI), although an activation of the TNF-α cytokine system may be linked to obesity and aging. Plasma levels of sTNF-Rs are associated with increased body weight,[20] and narcoleptic patients tend to have a higher BMI compared with controls.[21,22]

Furthermore, a small number of studies suggest that certain cytokine-producing genes may predispose to narcolepsy. Hohjoh et al[23] conducted a study of the association between TNF-R p75 polymorphisms and human narcolepsy and found that the 196 R allele was significantly more frequent in narcoleptic patients, suggesting that this allele is associated with susceptibility to narcolepsy. However, Wieczorek et al[24] could not confirm these results in European narcoleptic patients. Despite these findings, to our knowledge, sTNF-R p55 and sTNF-R p75 plasma levels have not been investigated in narcoleptic patients, although they play a crucial role in modulating the in vivo biological activity of TNF-α.[25]

METHODS

SUBJECTS

Thirty patients with narcolepsy and 120 sex- and age-matched and 101 sex-, BMI- and age-matched controls were included in the present study.

During an annual meeting of the German Narcoleptic Society in October 2005, we included 59 patients in the study. The German Narcoleptic Society is a self-help group of narcoleptic patients in Germany. All patients were physically examined and a medical history was taken. Blood was drawn after an overnight fasting between 6 and 10 hours, and body weight and height were measured. Patients completed the Epworth Sleepiness Scale (ESS). We contacted treating physicians to confirm the diagnosis of narcolepsy in the patients. The diagnosis of narcolepsy according to the International Classification of Sleep Disorders (ICSD) criteria could be verified in 30 patients.

In these patients, the mean±SD ESS score was 18±4. Patients took the following medications: among the psychostimulants, 11 patients were taking modafinil, 5 were taking methylphenidate hydrochloride, and 1 was taking fenethylline hydrochloride; 3 patients were taking the adrenergic agonist ephedrine hydrochloride; 1 patient was taking the new anticataplectic medication γ-hydroxybutyrate; and among the antidepressants, 2 patients were taking venlafaxine hydrochloride, 2 were taking citalopram hydrochloride, 1 was taking sertraline hydrochloride, and 1 was taking fluoxetine hydrochloride.

We matched these patients to controls from the Bavarian Nutrition Survey II (BVS II). The BVS II is a representative study of the Bavarian population (N=1050). Subjects were recruited by a random route sampling procedure from the German-speaking Bavarian population. This recruitment procedure included the selection of 42 communities as so-called sampling points, a random walk with a given start address, and a random selection of 1 household member. Within 6 weeks after recruitment, all adult study subjects (age ≥18 years) were invited to their nearest health office for blood sampling and standardized anthropometric measurements. A subsample of 568 persons followed this invitation and participated in anthropometric measurements and blood sampling similar to the procedure applied in the narcolepsy project. Because of technical reasons, only 558 blood samples from these controls could be analyzed regarding TNF-α and its soluble receptors. All participants of both study groups gave their written informed consent. The studies were approved by an independent local ethics committee.

PROCEDURE

Blood was stabilized with sodium EDTA (1 mg/mL) and aprotinin (300 kIU/mL) and immediately centrifuged, and the plasma was frozen to −20°C. Tumor necrosis factor α and sTNF-R p55 and sTNF-R p75 plasma concentrations were measured using commercial enzyme-linked immunosorbent assays (Biosource, Brussels, Belgium). For all assays the intra-assay and interassay coefficients were below 7% and 9%, respectively.

DATA ANALYSIS

We matched up to 4 subjects from the BVS II sample to 1 narcoleptic patient according to sex and age. Matching criteria were the same sex and ±1 year of age. In a second step, we matched up to 4 controls to 1 narcoleptic patient according to sex, BMI, and age. Respective to the narcoleptic patient, matching criteria were the same sex, BMI ±5%, and age ±10 years. For 11 narcoleptic patients, fewer than 4 control subjects could be found according to these matching criteria (3 controls for 4 patients, 2 controls for 6 patients, and 1 control for 1 patient).

Cytokine levels were compared between narcoleptic patients and controls using a linear mixed model with a random intercept for each group consisting of 1 narcoleptic patient and his or her matched control. This allows for exploring the differences between the narcoleptic subjects and controls within each group of matched subjects while taking the variability between the control subjects into account and allowing for an unequal number of control subjects for each patient. In both the age-matched and the BMI- and age-matched samples, we assessed differences between groups (narcoleptic patients vs controls) and possible group × sex interaction effects. For the age-matched sample we also analyzed group and group × sex interaction effects after controlling for differences in BMI.

In the complete BVS II population sample, the distribution of cytokine levels was tested for normality using the Kolgomorov-Smirnov (K-S) test, and suitable transformations across the ladder of powers were sought to achieve normality of the data and thus allow for parametric modeling including the evaluation of possible interaction effects. None of the parameters (TNF-α, sTNF-R p55, and sTNF-R p75) had a normal distribution (K-S test, $P<.05$), and all were significantly skewed. Log_{10} transformations were used to normalize the distribution for TNF-α (K-S test, $P=.22$) and sTNF-R p55 (K-S test, $P=.23$), whereas for sTNF-R p75 a power transformation with −1 resulted in a normal distribution of sTNF-R p75 (K-S test, $P=.33$).

RESULTS

When comparing narcoleptic patients with sex- and age-matched controls, narcoleptic patients showed a significantly higher BMI compared with normal controls of the same age and sex (**Table 1**).

In the sex- and age-matched and the sex-, BMI-, and age-matched samples, narcoleptic patients did not differ from controls in TNF-α levels (**Table 2**). Patients had higher sTNF-R p55 levels compared with their sex- and age-matched controls, but the difference was apparent only in female participants (group × sex interaction, Table 2). However, compared with the sex-, BMI-, and age-matched sample, this difference was not statistically significant.

Soluble TNF-R p75 levels were consistently elevated in the narcoleptic patients compared with their sex- and age-matched as well as sex-, age-, and BMI-matched counterparts. Again, this difference was mostly apparent in female participants; however, a group × sex interaction was only found in the sex- and age-matched sample (Table 2).

Table 1. Characteristics of Study Participants

Characteristic	Narcoleptic Patients	Matched Samples	
		S/A-MC	S/A/B-MC*
No.	30	120	101
M/F	9/21	36/84	34/67
Age, mean ± SD, y	49.20 ± 16.59	49.21 ± 16.40	49.48 ± 15.53
BMI, mean ± SD	29.11 ± 4.49	26.29 ± 4.55	29.20 ± 4.49
Comparison between narcoleptic patients and controls, F score (*P* value)	. . .	BMI: $F_{1,119}$ = 9.99 (.002)	Age: $F_{1,100}$ = 0.31 (.58)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); S/A/B-MC, sex-, age-, and BMI-matched controls; S/A-MC, sex- and age-matched controls.

*For 11 narcoleptic patients, there were fewer than 4 control subjects. For that reason, age and BMI values are weighted summary statistics.

COMMENT

In the present study, we found a significantly higher BMI in narcoleptic patients compared with controls. Soluble TNF-R p75 levels were consistently elevated in the narcoleptic patients compared with their sex- and age-matched as well as sex-, BMI-, and age-matched counterparts, while the difference in sTNF-R p55 plasma levels between groups disappeared when matching according to the BMI. Levels of TNF-α did not differ significantly between the group of narcoleptic patients and the 2 control groups.

Using the present data, we could confirm that narcoleptic patients exhibit a significantly higher BMI compared with controls.[12,21] Regarding TNF-α levels, previous studies revealed conflicting results,[18,19] possibly because, in contrast to the present study, controls in these studies were not matched by sex, age, and BMI. Regarding sTNF-R p55 and sTNF-R p75 plasma levels in narcoleptic patients, no comparable data are available to our knowledge.

Possible causes of elevated sTNF-R plasma levels in narcoleptic patients could be due to differences in age, BMI, genetics, and/or disease-related activation of the TNF-α system. We could exclude age-, sex-, and BMI-related causes for differences in sTNF-R p75 plasma levels because sTNF-R p75 levels were consistently elevated in the narcoleptic patients, even when comparing sTNF-R p75 plasma levels with their sex-, BMI-, and age-matched counterparts.

One reason for sTNF-R p75 plasma level elevation in narcoleptic patients would be genetic differences such as TNF-R p75 gene polymorphisms, though previous results regarding the frequency of certain alleles are conflicting.[23,24] Another reason for sTNF-R p75 plasma level elevation in patients with narcolepsy may be HLA-DR2 differences between narcoleptic patients and controls. However, HLA-DR2–positive narcoleptic subjects[4,5] have been shown to have lower TNF-α plasma levels in vivo,[26] and to our knowledge no literature is available regarding sTNF-R plasma levels and HLA-DR2 differences.

It could also be the case that sTNF-R p75 plasma levels are elevated secondary to other aspects in narcoleptic patients caused by differences regarding the leptin[27] or hypocretin[8] system or caused by the medication patients take. Comparable obese nonnarcoleptic subjects, however, are reported not to show an association between leptin and sTNF-R p75 plasma levels[28] or even show a positive correlation between leptin and sTNF-R p75 plasma levels.[29] However, because narcoleptic patients were reported to have decreased leptin levels,[27] one would expect these patients to have even decreased sTNF-R p75 plasma levels. To our knowledge, no data exist regarding the influence of decreased hypocretin production on sTNF-R p75 plasma levels.

It is unlikely that the psychotropic medication taken by the patients is responsible for the elevation of sTNF-R levels because stimulants such as modafinil, which was the preferred drug in the investigated narcoleptic sample, are not known to activate the TNF-α system. On the contrary, tricyclic and tetracyclic antidepressants,[30] atypical neuroleptics,[31] and mood stabilizers[32] leading to daytime sleepiness are reported to activate the TNF-α system and to raise sTNF-R p55 and sTNF-R p75 plasma levels, whereas psychotropic drugs not leading to daytime sleepiness such as venlafaxine[30] do not result in elevated sTNF-R p55 and sTNF-R p75 plasma levels. Therefore, the elevation of sTNF-R p55 and sTNF-R p75 plasma levels due to the administration of drugs leading to daytime sleepiness appears as an experimental model for the association between sTNF-R p55 and sTNF-R p75 plasma levels and sleepiness.

Questioning the possible functional significance of our findings leads to remarkable metabolic aspects of narcoleptic patients; levels of sTNF-Rs, known to be involved in the regulatory endocrine system of body adiposity independently of leptin and resistin axis in nonmorbidly obese patients,[28] are elevated in obese subjects,[20] and sTNF-R levels are reported to be associated with type 2 diabetes mellitus independently of body weight.[33] Tumor necrosis factor signaling is known to lead to diabetes by decreasing insulin receptor signaling capacity and

Table 2. Plasma Concentrations of TNF-α and Its Soluble Receptors in Narcoleptic Patients and Normal Controls

Parameter/Sample	Subjects*			Difference Between Groups†			
						Controlled for BMI	
	All	Male	Female	Group	Group × Sex	Group	Group × Sex
TNF-α, pg/mL							
Patients with narcolepsy	30 (9.39) [8.58]	9 (9.04) [7.31]	21 (9.75) [9.24]	. . .	. . .	. . .	. . .
S/A-MC	120 (10.84) [6.24]	36 (11.57) [4.69]	84 (10.58) [6.57]	$F_{1,119}$ = 1.35 (.25)	$F_{1,118}$ = 3.60 (.06)	$F_{1,118}$ = 1.76 (.19)	$F_{1,117}$ = 3.36 (.06)
S/A/B-MC‡	101 (10.58) [5.30]	34 (10.49) [4.65]	67 (10.58) [4.88]	$F_{1,100}$ = 2.49 (.12)	$F_{1,99}$ = 1.53 (.22)	. . .	. . .
sTNF-R p55, ng/mL							
Patients with narcolepsy	30 (1.96) [0.59]	9 (1.93) [0.41]	21 (2.03) [0.59]	. . .	. . .	. . .	. . .
A-MC	120 (1.77) [0.64]	36 (2.10) [0.46]	84 (1.66) [0.50]	$F_{1,119}$ = 6.43 (**.01**)	$F_{1,118}$ = 9.83 (**.002**)	$F_{1,118}$ = 1.86 (.17)	$F_{1,117}$ = 7.83 (**.006**)
A/B-MC‡	101 (1.84) [0.49]	34 (1.86) [0.65]	67 (1.84) [0.42]	$F_{1,100}$ = 1.62 (.21)	$F_{1,99}$ = 1.21 (.27)	. . .	. . .
sTNF-R p75, ng/mL							
Patients with narcolepsy	30 (5.47) [1.41]	9 (4.81) [1.21]	21 (5.54) [1.21]	. . .	. . .	. . .	. . .
A-MC	120 (4.38) [1.59]	36 (5.52) [1.71]	84 (4.15) [1.19]	$F_{1,119}$ = 16.36 (**.001**)	$F_{1,118}$ = 10.33 (**.001**)	$F_{1,118}$ = 9.30 (**.003**)	$F_{1,117}$ = 9.34 (**.003**)
A/B-MC‡	101 (4.49) [1.60]	34 (4.90) [1.52]	67 (4.37) [1.58]	$F_{1,100}$ = 8.94 (**.003**)	$F_{1,99}$ = 1.11 (.29)	. . .	. . .

Abbreviations: A/B-MC, age- and BMI-matched controls; A-MC, age-matched controls; BMI, body mass index; S/A/B-MC, sex-, BMI-, and age-matched controls; S/A-MC, sex- and age-matched controls; sTNF-R, soluble tumor necrosis factor receptor; TNF-α, tumor necrosis factor α; ellipses, not applicable.
*Data are given as number (median) [interquartile range].
†Data are given as F score (*P* value). The values in boldface represent statistical significance.
‡For 11 narcoleptic patients, there were fewer than 4 control subjects. For that reason age and BMI values are weighted summary statistics.

insulin sensitivity and to induce brown adipose tissue atrophy and β3-adrenoreceptor deficiency.[34] Therefore, the elevation of sTNF-R p75 plasma levels in narcoleptic patients is in line with the known impaired glucose tolerance in this group of patients.[35]

Although soluble forms of cytokine receptors such as sTNF-R p75 are thought to control cytokine activity in vivo by inhibiting the ability of cytokines to bind to their membrane receptors and thus inhibiting a biological response,[25] elevated plasma levels of sTNF-R p75 indicate an inflammatory process in several diseases, for example, rheumatoid arthritis.[36] Soluble TNF-Rs are soluble variants of the extracellular domains of their membrane-bound form derived by the proteolytic actions of a disintegrin metalloproteinase called TNF-α–converting enzyme[37] and may therefore be associated with the amount of membrane-bound sTNF-R p75, which is able to induce thymocyte[38] and T-cell proliferation[39] as well as apoptosis.[40]

One limitation of the study is that no specific screening instrument for sleep apnea syndrome was applied. Because narcoleptic patients showed a higher BMI compared with the sex- and age-matched controls, sleep apnea is related to being overweight, and sleep apnea can affect inflammatory markers.[14] To rule out BMI-related effects, we compared the patients with the sex-, BMI-, and age-matched controls.

In conclusion, we investigated a sample of narcoleptic patients in comparison with normal controls. Narcoleptic patients showed increased plasma levels of sTNF-R p75, suggesting a functional alteration of the TNF-α cytokine system and further corroborating a possible pathogenetic role of the immune system in this sleep disorder. These results highlight the important relationship between sleep and sleep disorders and immune function.

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