Narcolepsy: Autoimmunity or Secondary to Infection?

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Autoimmunity • Infection • Tumor necrosis factor alpha • Humen leukocyte antigen

Narcolepsy is a sleep disorder that is characterized by excessive daytime sleepiness, cataplexy, hypnagogic hallucination, and sleep paralysis. In the review presented here, we aim at focusing on the immunological aspects of the disease.

Special attention will be given to the link between tumor necrosis factor-α (alpha) (TNF) and major histocompatibility class II (MHC II) antigens and on autoimmunity, autoinflammation, and neuronal cell death. The latter may affect mainly neurons that produce hypocretin peptides (*Hcrt-1* and *Hcrt-2*; also known as orexins A and B) and hypocretin receptors (*Hcrtr-1* and *Hcrtr-2*). The involvement of this neurotransmitter pathway in narcolepsy is extensively discussed within this book.

A mutation in the canine *Hcrtr-2* gene or disruption of the prepro-hypocretin gene in knockout mice causes narcolepsy. In humans, only one patient with early onset of disease in childhood has been reported to have a mutation in the hypocretin genes. However, hypocretin concentration in the cerebrospinal fluid (CSF) of narcolepsy patients is decreased. This finding points to an abnormal expression of the *Hcrt* gene, or release of hypocretin in the disease.

TNF and Its Receptors: Essential in the Pathogenesis of Narcolepsy?

A growing list of evidence supports a role of the cytokine TNF in sleep disorders including narcolepsy, daytime fatigue in infectious and autoimmune diseases, and sleep apnea. TNF is a homotrimeric cytokine that binds to two receptors: TNFRI and TNFRII. TNF is mainly produced by monocytes, macrophages, and dendritic cells. In the context of sleep disorders, it is of note that TNF is also produced in the central nervous system (CNS), mainly by microglial cells and astrocytes.

After synthesis in the endoplasmic reticulum, TNF is trafficked to the cell membrane. There the cytokine either acts as a membrane protein, or is cleaved by the TNF-converting enzyme TACE. Antibodies to TNF (infliximab or adalimumab) and soluble TNFRII (etanercept) prevent the binding of TNF to their membrane receptors and thereby interfere with the physiological function of TNF in the host response to infection and tumor defense. However, anti-TNF strategies have also

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become a main line in the treatment of autoimmune diseases, including rheumatoid arthritis.

TNF is a pleiotropic inflammatory cytokine that acts on parenchymal cells in various organs including the CNS. There it modulates the function of microglia, oligodendrocytes, astrocytes, and neurons. In the context of sleep disorders, it is of note that TNF activates the production of glutamate by microglial cells [1, 2]. In cocultures of microglial and cerebellar granule cells, glutamate is the main effector molecule that leads to apoptosis of the neurons.

Detoxification of glutamate is achieved by astrocytes, the function being impaired by glucose oxidase, an enzyme that maintains steady-state levels of hydrogen peroxide. Thus, a possible mechanism whereby TNF alters neuronal function and causes neuronal injury is by its action on the production of excitatory amino acids by macrophages invading the CNS and resident microglia, and the prevention of the function of astrocytes in glutamate detoxification and balancing the electrolyte concentration. When discussing the potential role of TNF in sleep disorders, studies on overexpression of TNF in the CNS are of importance. Transgenic mice which overexpress TNF in the CNS lead to activation of macrophages/microglia, apoptosis of oligodendrocytes, demyelination, and axonal damage, the effect being mediated through the activation of TNFR1 [3].

Besides its role in inflammation and its response to infection, much interest has been gained in the role of TNF in sleep regulation (see review [4]). TNF has been identified to promote non-rapid eye movement sleep (NREM) and EEG delta (1/2–4 Hz) power, an index of sleep intensity. The same effect is seen with IL-1 when injected systemically or intracerebroventricularly. On the contrary, antibodies to these cytokines or their soluble receptor, as well as the IL-1 receptor antagonist (IL-1RA), interfere with spontaneous sleep [5].

These findings are of enormous importance for the understanding of dysfunction of sleep regulation in inflammatory and autoimmune disorders and in stress, because these conditions are associated with increased expression of TNF and IL-1. However, these cytokines are also claimed to play a role in normal, physiological sleep. The expression of both cytokines shows a circadian rhythm, with the highest levels in the brain and blood correlating with high sleep propensity. In rats, TNF bioactivity increases up to five times at 6 p.m. compared to that at 12 a.m. and 12 p.m. [6]. Failure of TNF signaling in TNFRI gene knockout mice and in TNFRI and RII double-deficient mice is associated with less NREM sleep [7, 8]. These findings in TNFRI knockout mice were not in agreement with another study [9]. The signals that lead to circadian regulation of TNF expression are not known. In this regard, it is interesting that ATP released at synapses during neurotransmission has been shown to act on purine Pz receptors and thereby promote the release of TNF from microglia [10]. Recently, a 72-h REM sleep deprivation in rats was associated with increased plasma levels of IL-1β (beta), TNF, and IL-17 [11]. Taken collectively, these data support a role of TNF and IL-1 in sleep regulation.

Studies on single nucleotide polymorphisms (SNPs) in cytokine genes in patients with autoimmune diseases, mainly type 1 diabetes and rheumatoid arthritis, point to an SNP in the TNF gene promoter position; that is, 308 G to A is found to be associated with increased TNF serum concentrations and high in vitro TNF transcription and expression [12, 13].

Since narcolepsy is strongly associated with the human leukocyte antigen (HLA) DQB1*0602, an autoimmune pathogenesis has been suggested. Together with the numerous reports on sleep regulation by cytokines, considerable interest has been paid to cytokines in narcoleptic patients. IL-1β (beta), IL-1RA, IL-2, TNF, and LTα (alpha) in plasma and in mitogen-stimulated monocytes and lymphocytes in narcoleptic patients were not found to differ from that in HLA-DR2-matched controls [14]. Only IL-6 was increased in LPS-activated monocytes. However, increased TNF and IL-6 serum levels compared to that in age- and gender-matched controls have been detected in a later study from Okun et al., who found TNF in patients' sera to be 13.9 ± 1.39 pg/ml (control: 8.2 ± 0.45 pg/ml) and IL-6 to be 6.7 ± 1.45 pg/ml (control: 0.49 ± 0.09 pg/ml) [15]. In the later

study, stimulatory drugs were associated with lower TNF levels. Thus, stimulatory drugs may influence cytokine levels in narcoleptics. As outlined above, genetic polymorphism in the *Tnf* promoter may also influence TNF serum concentrations. The T-cell allele of the C-857T polymorphism was strongly associated in the subgroup of DRB1*15/16 (HLA-DR2 type)-negative patients [16]. This is interesting because elevations of both TNF and IL-6 have been reported in subjects who are sleep restricted, either experimentally or naturally by insomnia [17]. An increase in TNF is also seen in patients with sleep apnea, the TNF concentrations being normalized by continuous positive pressure [18]. In an acute animal model of obstructive sleep apnea, oxygen desaturation and respiratory effort were followed by an increase in TNF and IL-1 [19]. In a recent study on sleep apneics, TNFRI but not TNF serum concentrations correlated with different forms of arousal, namely, snore and spontaneous arousal, and periodic limb movement arousal (TNFRII was not assessed) [20].

Our laboratory has shown that subcutaneous infusion of TNF impairs locomotor activity of mice and lowers the expression of clock genes in the liver. TNF acts on the clock genes that are regulated by E-boxes in their promoters, namely, the PAR bZip clock-controlled genes *Dbp*, *Tef*, and *Hlf* and the period genes *Per1*, *Per2*, and *Per3*, but neither *Clock* nor *Bmal1* which do not have E-boxes in their regulatory DNA sequences [21]. Since clock genes are central in the sleep–wake cycle and mapped to mouse chromosome 5 within a region syntenic to the human chromosome 4g12, a region close to the narcolepsy susceptibility locus 4p/3-q21 identified recently, polymorphisms have been analyzed in the clock gene [22]. However, no differences in allelic and genotypic frequencies of two clock polymorphisms have been observed in narcoleptics compared to controls. One of the clock gene polymorphisms has been found to be associated with sleep genotypes [23].

In a well-controlled recent study, new information has been obtained by Himmerich et al. [24]. Whereas TNF was not increased, narcoleptic patients have higher TNFRII (but not sTNFRI) compared to controls. This may be explained by genetic polymorphisms. Positive correlations have been identified of TNF (−857T) and TNFRII (−196T) combination with narcolepsy (and DRB1*1501 and TNF (−857T) [25, 26]). Further studies should address the relationship of sTNFRII and HLA-DR2. Taken collectively, there is clear evidence that TNF and TNFR serum concentrations are influenced by many variables including obesity, stimulatory drugs, stress, oxygen saturation, *Tnf* gene polymorphism, and the HLA-DQB1*0602 allele. Thus, large population studies are required to control for these multivariable influences.

Anti-self T Lymphocytes and Activation of Macrophages/Microglial Cells: Key Factors in Narcolepsy?

Narcolepsy is genetically characterized by strong linkage to the HLA complex. More than 90% of the patients have the HLA-DR2 haplotype DQB1*0602. These data may point to an autoimmune mechanism. From a clinical point of view, a given autoimmune disease is often associated with other autoimmune diseases in the affected individual or in the family of the patient. However, there is no strong evidence for such a clustering of autoimmune diseases in narcolepsy. Unlike other autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, or Sjögren syndrome, autoantibodies such as antinuclear antibodies, rheumatoid factor, and antibodies to nDNS, SS-A, Sm, and histone are not increased in narcolepsy [27]. Patient's markers indicating inflammation, such as increased blood sedimentation and C-reactive protein, are not found to be abnormal. Thus, these clinical data do not support a role for autoimmunity in narcolepsy.

Hallmarks of the T-cell system in autoimmune diseases are the demonstration of T cells sensitized to self-antigens, dysregulated CD4 effector T cells, e.g., CD4-TH17 cells, low regulatory T cells, and inflammation at sites of the

autoimmune attack in distinct organs. The inflammation is characterized by local accumulation of CD4+ T cells and proinflammatory macrophages, with increased expression of MHC II and cytokines. None of these characteristic features of T-cell autoimmunity have been assessed in detail in narcolepsy.

In a highly interesting new study on T-cell receptor-alpha (TCRα), or -beta (β) subtypes, 807 narcolepsy patients positive for HLA-DQB1*0602 and hypocretin deficient, and 1,074 controls were selected for a genome-wide association study. The data identified an association between narcolepsy and polymorphisms in the T-cell receptor alpha [TRAα] locus. TRAα is expressed by T cells and interacts with HLA class I CD8 T cells and on CD4 cells with the HLA class II including the DQα β heterodimer denoted DQ 0602, which encodes for DQB1*0602 and DQA1*0102 alleles. Somatic cell recombination in the TRAα and TRBα loci leads to a diverse repertoire of distinct TCRα β idiotype-bearing T cells. Since narcolepsy is almost exclusively associated with a single HLA allele – DQB1*0602, the authors suggest that the polymorphism detected could influence VJ2 recombinations that bind DQ0602 and mediate autoimmunity to Hcrt neurons [28].

Since in autoimmune diseases histological examination reveals cellular infiltrates of lymphocytes, plasma cells, and macrophages in areas of tissue destruction, it is of importance whether this is seen in narcolepsy. Where should one observe? As outlined in this book, special attention should be given to Hcrt-1- and Hcrt-2-producing neurons in the hypothalamus and in the Hcrt projection fields. Since the disease has a good life expectancy, histological workup of brains is hardly available. In a patient with an *Hcrt* mutation and early-onset narcolepsy (age 6 months) and a long follow-up over many years, histological analysis did not show "obvious lesions" or gliosis in the perifornical area. Most importantly, immune histochemical staining of HLA-DR disclosed normally distributed resting microglia in both white and gray matter of two narcoleptic subjects. None of the cases were associated with activated, ameboid microglia. This is remarkable since upregulation of HLA-DR and transition from resting ramified microglia are hallmarks of immune-mediated inflammation in the CNS. In the context of the aforementioned discussion on dysregulated TNF expression, it is interesting that in situ hybridization of TNF did not produce significant signal in control and narcoleptic tissue [29]. Taken collectively, these findings do not support the idea of a T-cell/macrophage-mediated destruction of the reduced hypocretin neurons detected in postmortem studies. Histological analysis and HLA-DR staining in four adult and three young narcoleptic Dobermans did not reveal lymphocyte infiltration or inflammation in the CNS in canine narcolepsy. However, young dogs aged 3 and 8 months have a concomitant disease-onset diffuse increase in MHC II antigens on microglia. MHC II expression in older narcoleptic dogs did not differ from that in controls. With age, a general increase in MHC II molecules can be observed in microglia [30]. The observation in dogs may indicate that MHC II pathology is seen early at the time of loss of Hcrt neurons.

Are Anti-neuronal Antibodies Involved?

Loss of hypocretin neurotransmission may be due to either impairment of production and/or secretion of Hcrt by neurons, or loss of Hcrt neurons. Several studies have addressed the hypothesis that autoantibodies may lead to alterations in the Hcrt system. No increased IgG index or oligoclonal bands were detected in the CSF of 15 patients with narcolepsy. These data speak against an intrathecal synthesis of autoantibodies by local plasma cells [31]. Recent studies have failed to detect antibodies against orexin or orexin receptors [32, 33], or also against hypothalamic neurons [34]. Antibodies to hypothalamic neurons were claimed in only one of nine patients, with the antibody epitope not being characterized [35]. A new potential autoimmune target has been identified recently: Insulin-like

growth factor-binding protein-3 (IGFBP3), which is expressed in hypocretin neurons and downregulated in narcolepsy. However, no anti-IGFBP3 antibodies were detected in human sera or CSF of patients. IGFBP3 concentration in CSF was not decreased [36].

Ex vivo mouse colonic migrating motor complex (CMMC) preparations are inhibited by IgG from narcoleptic patients. In this system, contractions migrating from proximal to the distal colon at 3- to 5-min intervals are recorded. The frequency of these contractions is severely interrupted or contractions even abolished by patient's IgG, but not by IgG from controls. The effect is not due to alterations of smooth muscle functions. Abrogation of contractions is followed by cholinergic myogenic hyperactivity. In the light of the effects found on the enteric nervous system, the authors wonder why there are no reports of abnormal colon movements in patients. The epitopes of the antibodies detected in the CMMC assay remain unclear and are unlikely to be Hcrt because orexin seems not to be present in the murine gut [37].

Even the detection of anti-neuronal antibodies in narcolepsy may not be indicative of immune-mediated damage of neurons. In paraneoplastic syndromes, autoantibodies are thought to be an epiphenomenon or footprint for autoimmunity, but are not directly involved in damage of the CNS. There are exceptions, such as autoantibodies directed against voltage-gated potassium or calcium channels located at nerve terminals, which may lead to paraneoplastic cerebellar degeneration and limbic encephalitis, respectively (for review, see [38]).

Conclusion and Hypothesis

The strong association of narcolepsy with HLA-DR2 and HLA-DQB1*0602 has provided strong interest in the hypothesis that narcolepsy is an autoimmune disease. However, several points about the aforementioned observations deserve emphasis. (1) Classical autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, or myasthenia gravis are not reported to be increased in narcoleptic patients and their families; (2) common autoantibodies against nuclear proteins are uncommon in sera of narcoleptic patients; (3) intrathecal synthesis and oligoclonal bands are not seen in the CSF; (4) there is no evidence of antibodies to hippocampal neurons, orexin, and orexin receptors in the disease; and (5) accumulation of T and B lymphocytes in the CNS, influx of monocytes from the blood, and activation of microglia in the tissue are – at least at late time points of the disease – not seen (Table 1).

Taking this into consideration, autoimmunity in narcolepsy becomes questionable. Difficulties in arriving at a suitable answer have been hampered by the fact that experiments demonstrating

Table 1 Autoimmunity in narcolepsy?

Pro	Contra
Association with HLA-DR2/DQB1*0602	No association with autoimmune diseases in patients with narcolepsy in their family (e.g., SLE, rheumatoid arthritis, and thyroiditis)
Polymorphism in the T-cell receptor-α (alpha) locus	
Dysregulation of TNF/TNF receptor system	
	No autoantibodies to nuclear proteins (antinuclear antibodies, anti-nDNS)
	No increase in IgG index and no oligoclonal bands in CSF
Autoantibodies to Trib2	No narcolepsy-specific antibodies (anti-neuronal, anti-Hcrt, and anti-Hcrtr)

T-cell immunity to hippocampal neurons or orexin require stringent conditions, including availability of T cells from blood and CSF at the onset of disease. Further work should examine whether there is (1) a restricted usage of T-cell receptor genes, (2) whether T-cell activation and neurotoxic effects of T cells from patients on cocultures exist with immortalized hippocampal neurons transfected with HLA-DR2 genes, and (3) whether signs of narcolepsy develop in SCID mice that express human HLA-DR2 genes and are injected with reactivated CD4+ T cells from narcoleptic patients.

Very recent studies, however, provide new evidence that autoimmunity, superantigen-mediated T-cell activation, and non-T-cell-mediated activation by MHC II signaling could be involved in narcolepsy. New data identified an association between narcolepsy and polymorphisms in the TCR locus [39]. Because narcolepsy is almost exclusively associated with a single HLA allele – DQB1*0602 – the authors of this study hypothesized that the TCR polymorphism could contribute to autoimmunity directed against hypocretin neurons. Furthermore, in another recent study in narcolepsy patients, autoantibodies to Tribbles homolog 2 (Trib2), which is expressed by hypocretin neurons and by many other neurons, have been detected in a subset of patients [40]. The authors suggested that Trib2 is an autoantigen in patients with narcolepsy. In summary, whereas HLA-DQB1*0602 might select for recognition of self-antigens – and thereby lead to autoimmunity – the polymorphism of the TCR (alpha) gene might be crucial in superantigen-mediated T-cell activation. For the detection/confirmation of anti-CNS antibodies, future studies may want to concentrate on patients with very recent onset of disease.

However, besides the hypothesis of autoimmune mechanisms, other explanations for the association of HLA-DR2 with narcolepsy have to be taken into consideration. At disease onset, microglia of narcoleptic patients are reported to overexpress MHC II antigens. TNF acts synergistically with interferon gamma (IFN-γ) to upregulate MHC II expression on microglia. In T-cell-mediated diseases of the CNS, such as multiple sclerosis or experimental autoimmune encephalomyelitis, the function of MHC II is primarily that of antigen presentation by microglia and macrophages. However, in diseases such as Huntington's disease and Parkinson's disease or brain trauma, the aforementioned types of cells express MHC II, but no evidence for T-cell involvement has been observed. It has been suggested that an alternative role for MHC II is in signal transduction, which leads to activation, differentiation, and production of proinflammatory cytokines in vitro. Cuprizone-induced oligodendrocyte dysfunction with T-cell independent demyelination pathology is much less pronounced in MHC II I-$A_{\beta\ (beta)}^{-/-}$ mice or in mice with a truncated I-$A_{\beta\ (beta)}$ which lacks a cytoplasmic domain. This phenotype was associated with limited microglia/macrophage activation and reduced production of TNF, IL-1β (beta), and nitric oxide, molecules known to exert T-cell-independent toxic effects on oligodendrocytes. It is not clear yet how MHC II is being activated in the absence of T-cell function [41, 42]. These findings may be of relevance in narcolepsy. As a hypothesis, infectious pathogens may have a tropism to hypothalamic orexin neurons and, therefore, cause these neurons to activate microglia to increase signaling by their MHC II molecules. Necrotic neurons have been shown to activate microglia to upregulate MHC II, costimulatory molecules (CD40 and CD24), β-2 integrin, CD11b, iNOS, and cytokines including TNF [43]. In the MyD88-dependent step, activated microglia induce neurotoxicity through upregulation of glutaminase, an enzyme that produces glutamate, which is an NMDA receptor agonist [1, 2, 43]. As a consequence, MHC II may trigger the production of toxic molecules which destroy orexin neurons (Fig. 1a). Alternatively, infectious pathogens expressed in the hypothalamus may act as superantigens and bridge TCR on T cells with MHC II on microglia, which become activated to secrete neurotoxic molecules, e.g., via glutamate production (see [2]). The narcolepsy-associated polymorphism of the TCRα locus and DQB1*0602 on microglia may be required for the initiation of the superantigen-dependent process (Fig. 1b).

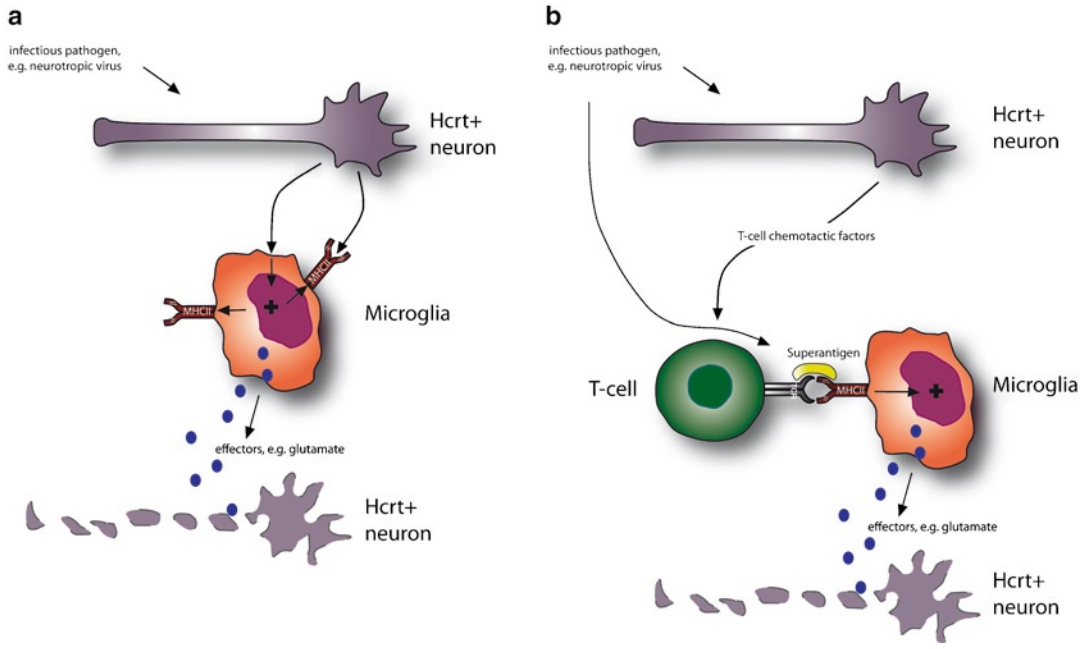

Fig. 1 Infectious pathogens lead to microglia-mediated toxicity of Hcrt-positive neurons. (**a**) Microglia-mediated T-cell-independent neurotoxicity. (**b**) Superantigen-induced microglia-mediated neurotoxicity

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