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The olfactory bulb: A link between environmental agents and narcolepsy, from the standpoint of autoimmune etiology

Isamu Mori

Faculty of Health and Nutrition, Shubun University, Ichinomiya, Aichi 491-0938, Japan

A B S T R A C T

Narcolepsy type 1 is a lifelong sleep disorder characterized by the loss of hypocretin-producing neurons in the brain. Environmental agents, including influenza, neurotoxic metals, and combustion smoke, have been implicated in the pathogenesis, especially in carriers of the human leukocyte antigen class II DQB1*06:02 allele. Sensitive experimental approaches have recently revealed hypocretin-autoreactive $CD4^+$ and $CD8^+$ T cells in the blood of narcoleptic patients. However, such potentially harmful cells are also detectable, to a lesser degree, in control DQB1*06:02 carriers, suggesting that the integrity of the blood–brain barrier (BBB) provides a neuroprotective effect. Here, we present the hypothesis that external toxic agents induce neuroinflammation in the olfactory bulb and concomitant overproduction of proinflammatory cytokines (e.g., tumor necrosis factor-α and interferon-γ); this, in turn, compromises the BBB, allowing autoimmune cells to access and kill hypocretinergic neurons. Such sequential pathological alterations could occur insidiously, passing unnoticed and consequently being underestimated. The elevated number of autoreactive T cells in narcoleptics relative to controls might reflect externally induced immunomodulation rather than a direct disease trigger.

Introduction

Narcolepsy type 1 (NT1) is a lifelong sleep disorder characterized by the loss of hypocretin (Hcrt)-producing neurons in the central nervous system [1]. The disease onset often occurs in childhood and adolescence, forcing patients to bear considerable physical, mental, and social burdens [2].

Various environmental factors are associated with onset of the disease, including influenza, neurotoxic metals, and smoking [3–5]. A previous report presented the hypothesis that such external agents invade and inflame the olfactory bulb (OB), triggering death of hypocretinergic neurons in the lateral thalamus that directly project axons to the OB [6]. Experimental evidence supports this simple hypothesis: in mice, intranasal instillation of H1N1 influenza virus leads to infection and inflammation of the OB, resulting in degeneration of hypocretinergic neurons and the onset of narcolepsy-like sleep disturbances [7]. Clinically, olfactory dysfunction is a common symptom of NT1, suggesting a neuropathology of the olfactory system [6].

On the other hand, disease incidence is tightly associated with the human leukocyte antigen (HLA) class II DQB1*06:02 allele [8]. By adopting sensitive detection systems, independent research groups have recently reported the presence of Hcrt-autoreactive $CD4^+$ and $CD8^+$ T cells in the blood of narcoleptic patients, solidifying the autoimmune etiology of NT1 [9–11]. However, autoimmune cells are also present, albeit in smaller numbers, in the blood of control DQB1*06:02 carriers. This phenomenon could be explained by the integrity of the blood–brain barrier (BBB) which confers neuroprotection from potentially harmful substances and cells [12].

Here, especially from the viewpoint of autoimmune etiology, we propose an additional hypothesis that environmental agents initiate neuroinflammation in the OB, concomitant with overproduction of proinflammatory cytokines; this compromises the BBB, enabling circulating autoimmune T cells to access and kill hypocretinergic neurons.

Hcrt-autoreactive T cells are detectable in the blood of DQB1*06:02 carriers

Latorre et al. reported that $CD4^+$ and $CD8\ T^+$ cells targeting self-antigens expressed on hypocretinergic neurons are present in the blood of NT1 patients, and found no evidence of molecular mimicry between Hcrt and influenza A H1N1 hemagglutinin (HA) [9]. Luo et al. detected a higher number of $CD4^+$ T cells recognizing Hcrt in the blood of narcoleptics than in control DQB1*06:02 carriers; in contrast to the results of Latorre et al., they did observe molecular mimicry between Hcrt and influenza H1N1 HA [10]. Pedersen et al. detected $CD8\ T^+$ cells recognizing Hcrt neuron–specific antigens in the blood of NT1 patients and controls carrying the DQB1*06:02 allele; the abundance of autoreactive cells was higher in the former [11]. Because neurons do not express HLA class II molecules, class I–restricted $CD8^+$ T cells appear to be the ultimate effectors, as shown in transgenic mice [13] and in the human brain [14]. Nevertheless, $CD4^+$ T cells can execute various effector functions, as exemplified by the pathogenesis of rheumatoid arthritis and other autoimmune disorders [15]. Taken together, these findings suggest that Hcrt-autoreactive T cells can circulate in

E-mail address: mori.i@shubun.ac.jp.

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healthy DQB1*06:02 carriers, but hypocretinergic neurons are protected from these potentially harmful cells by the BBB [12].

Environmental agent–induced OB inflammation may disrupt the BBB

The OB provides an efficient port for neuroinvasion by external factors [6]. Airborne agents can be nonspecifically taken up by dendritic nerve endings of olfactory neurons and transported to the OB, and olfactory ensheathing cells play an auxiliary role in the transportation [16]. Even non-neurotropic viruses can invade and inflame the olfactory network, as epitomized by influenza viruses [16–19]. Alternatively, because the olfactory mucosa lacks a barrier architecture equivalent to the BBB [20], environmental factors, such as the neurotoxic metal bismuth, can hematogenously reach olfactory neurons and subsequently spread to the olfactory network [21]. Furthermore, chronic exposure to neurotoxic metals, combustion smoke, and air pollutants can cause neuroinflammation in the OB [6,22–24]. Children and adolescents are more susceptible than adults to these indiscernible insults [24].

Upon external stimuli, microglia in the olfactory network produce proinflammatory cytokines, including TNF-α and IFN-γ [16,17,25,26]. These bioactive substances are translocated via endothelial cells from the brain parenchyma to the blood, and vice versa [26]. Notably in this regard, proinflammatory cytokine levels are significantly elevated in the blood of narcoleptics [27–29]. Most importantly, TNF-α and IFN-γ can enhance BBB permeability by downregulating tight junction proteins such as claudin-5 and occludin, thereby promoting the transendothelial migration of T cells [30–34] and enabling autoimmune cells to enter the brain parenchyma. This sequence of pathological events can happen in a covert fashion, leading to its potential underestimation by researchers in medical science fields.

Additionally, the higher abundance of Hcrt-autoreactive T cells in narcoleptics relative to DQB1*06:02 controls [10,11] may reflect environmental agent–related immunomodulation rather than the disease trigger. Proinflammatory cytokines, such as IFN- γ, can directly act on T cells, thereby increasing their abundance [35].

Hypothesis

1. In DQB1*06:02 carriers, T cells are primed to Hcrt by unidentified mechanisms; thus far, molecular mimicry between influenza HA and Hcrt remains the leading candidate. Hcrt-producing neurons are protected from these autoimmune cells by the integrity of the BBB. Consequently, NT1 does not develop.
2. Environmental agents invade the OB and initiate neuroinflammation in the olfactory network. Proinflammatory cytokines overproduced by microglia compromise the BBB, enabling autoreactive T cells in the blood to access and kill hypocretinergic neurons, culminating in the onset of NT1.
3. The chronology of the two pathophysiological events varies among patients: T cell priming for Hcrt may precede BBB disruption, and vice versa. Influenza may provide the two ‘hits’ in parallel.
4. Environmental factor–related neuropathology could take place in a silent manner, passing unnoticed and consequently being underestimated.
5. The greater abundance of autoimmune T cells in narcoleptics relative to controls may reflect environmental agent–related immunomodulation rather than the NT1 trigger.

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Declaration of Competing Interest

The author declares no conflict of interest related to this work.

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