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The olfactory bulb: A link between environmental agents and narcolepsy

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A B S T R A C T

Narcolepsy with cataplexy is a lifelong sleep disorder associated with orexin/hypocretin deficiency in the central nervous system. In addition to a genetic predisposition, a variety of environmental factors, such as influenza viruses, have been implicated in the pathogenesis of the disease. In this article, a hypothesis is proposed that environmental agents access the olfactory bulb and trigger neuroinflammation, which in turn induces neurodegeneration of orexinergic neurons in the lateral hypothalamus and other neuronal subpopulations regulating the sleep-wake cycle, which triggers the development of narcolepsy.

Introduction

Narcolepsy with cataplexy is a lifelong sleep disorder that is related to orexin/hypocretin deficiency in the central nervous system (CNS) [1]. Neuropathologically, narcoleptic brains display significantly reduced numbers of orexinergic neurons in the lateral hypothalamus (LH) [2,3]. The disease is unequivocally associated with the human leukocyte antigen (HLA) class II DQB1*06:02 haplotype; however, the immune mechanism involved in the neurodegenerative process remains unresolved [4]. Polymorphisms in the gene encoding for the T-cell receptor α chain could also play a role in narcolepsy with cataplexy [5].

In addition to a genetic predisposition, environmental factors have been shown to play significant roles in the neuropathogenesis of narcolepsy [6]. Research has suggested an association between disease onset and influenza vaccination during the 2009–2010 influenza A H1N1 virus pandemic [7]. It should also be noted that influenza virus infection itself was previously suggested to confer the risk of narcolepsy [8], and a seasonal outbreak of narcolepsy took place following the 2009–2010 H1N1 pandemic in China, independent of the H1N1 vaccination campaign [9]. Moreover, streptococcal infections may also be an environmental trigger for narcolepsy [10]. Apart from infectious agents, exposure to specific toxins, including metals, and second-hand smoke predispose individuals with HLA DQB1*06:02 to narcolepsy [11,12].

This article proposes a simple hypothesis that environmental agents gain access to the olfactory bulb (OB) and induce neuroinflammation, which leads to the degeneration of orexinergic neurons in the LH via direct anatomical connections with the OB, and thus to the development of narcolepsy.

The OB: An interface between environmental agents and orexinergic neurons

After external exposure, airborne agents in the upper nasal cavity can be nonspecifically taken up by dendritic nerve endings of olfactory neurons and transported to the OB [13,14]. A wide variety of viruses, even those that are not neurotropic, come into direct contact with the OB [13,14]. Of note, the influenza A virus has been demonstrated to invade the human CNS via this direct route [15]. Further, olfactory ensheathing cells could also transport environmental agents including microbes to the OB [14,16]. Alternatively, because the olfactory mucosa lacks a barrier structure equivalent to the blood-brain barrier of the CNS, environmental factors may hematogenously reach olfactory neurons that are subsequently transported to the OB [17]. For instance, viruses with viremic potential can infect olfactory neurons via the hematogenous route [14,17]. Similarly, this indirect route is supported by evidence that bismuth, a neurotoxic xenobiotic metal, readily diffuses from the fenestrated blood vessels of the olfactory mucosa after intraperitoneal injection and accumulates in the vicinity of these microvessels in mice [18]. Indeed, the metal travels along the olfactory route centripetally to the OB and further to structurally related nuclei of the brain.

Once in the OB, foreign agents, and the resulting neuroinflammation, could affect retrogradely connected orexinergic neurons in the LH since these neurons innervate the mitral and granule cell layers of the OB [19] (Fig. 1). Neurons in the LH producing melanin concentrating hormone (MCH), which is implicated in the regulation of rapid eye movement sleep, could also be affected by environmental agents [20]. In addition, these environmental agents and induced neuroinflammation may also affect other nuclei projecting to the OB including the cholinergic basal forebrain (BF), histaminergic tuberomammillary nucleus (TMN), serotonergic dorsal raphe (DR), and noradrenergic locus

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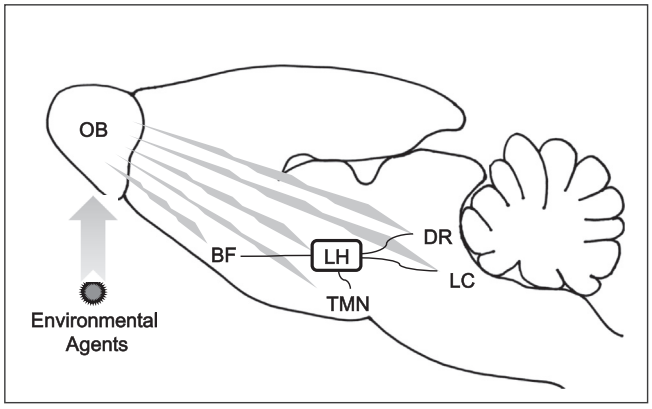

Fig. 1. Schematic depiction of subcortical sleep-wake regulators potentially targeted by environmental agents. Environmental agents can access and cause inflammation in the olfactory bulb (OB). Neuroanatomical links with the OB triggers the degeneration of sleep-wake regulating nuclei including LH (orexinergic and melanin-concentrating hormone-producing), BF (cholinergic), TMN (histaminergic), DR (serotonergic), and LC (noradrenergic). Neurodegeneration of the BF, TMN, DR, and LC could lead to secondary effects on orexinergic neurons in the LH and intricately modify clinical features of narcolepsy (see details in text). OB, olfactory bulb; LH, lateral hypothalamus; TMN, tuberomammillary nucleus; BF, basal forebrain; DR, dorsal raphe; LC, locus coeruleus.

coeruleus (LC) [21], which are all involved in wakefulness-promoting functions as in the case of the orexin system [20] (Fig. 1).

Providing further support of the link between environmental agents and orexinergic neurons, Tesoriero et al. clearly demonstrated that the mouse-neuroadapted strain of influenza A H1N1 virus infected the OB following intranasal inoculation of mice with targeted deletion of recombinant activating gene 1, lacking both T and B cells [22]. The virus successively targeted neurons expressing orexin and MCH in the LH as well as those in the BF, TMN, DR, and LC, inducing neurodegeneration. Affected mice presented narcolepsy-like sleep disturbances shown by experiments using electroencephalography and electromyography [22]. Taken together, the OB provides a potential link between environmental factors and orexinergic neurons. In this context, it is noteworthy that olfactory dysfunction is a common symptom of patients with narcolepsy [23–25].

Toxins in the OB: A latent destroyer of the orexin system

Various kinds of neurotropic viruses invade the CNS through the olfactory conduit and induce neuronal cell death [13,14,22,26]. It is also suggested, however, that common respiratory viruses with no neurotropic properties insidiously induce neuroinflammation in the olfactory network and initiate subsequent neurodegeneration in the CNS [16,27,28]. Proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) for instance, mediate the induction of neuronal cell death in vitro as well as in vivo [29,30]. In addition, chronic exposure to neurotoxic metals such as mercury, lead, arsenic, and bismuth could trigger neuroinflammation accompanied by neuronal cell death [31–35]. Moreover, continuous exposure to combustion smoke and air pollutants can cause neuroinflammation in the OB and subsequent neurodegeneration [36,37]. Upon exogenous activation, microglia in the OB initiate production of proinflammatory cytokines to trigger neurodegeneration [38]. It is notable that the blood levels of proinflammatory cytokines including TNF-α are increased in narcoleptic patients, suggesting the presence of chronic inflammation in the body [39,40]. These findings support a mechanism where exogenous toxic substances, once in the OB, may cause neurodegeneration of the orexinergic system directly and indirectly by inducing neuroinflammation.

To lend further support to this hypothesis for narcolepsy, neurons in the BF may promote arousal in concert with orexinergic neurons [41], serotonergic neurons in the DR could inhibit cataplexy [42], and noradrenergic neurons in the LC could consolidate wakefulness [42,43]. Furthermore, histaminergic TMN may compensate for the orexin system dysfunction [44]. Hence, affected BF, DR, LC, and TMN may confer secondary effects on orexin system functions and intricately modify clinical features of narcolepsy.

Hypothesis

Environmental agents gain access to the OB via a peripheral or hematogenous route, accumulate, and cause inflammation in the OB. Based on the direct connectivity, toxic agents in the OB and induced neuroinflammation degenerate orexinergic neurons in the LH and other sleep-wake regulators. Thus, the OB provides a pathway between environmental agents and narcolepsy.

Future direction

As mentioned above, accumulating evidence suggests significant roles of environmental factors in the neuropathogenesis of narcolepsy. Notwithstanding, further studies should be carefully executed given the elusive nature of disease incidence. First, the incubation period of narcolepsy could be longer than reported [9]. Second, unnoticed exposure to potentially toxic agents might be more frequent than expected [8,36,37]. Third, the incidence of the disease could be underestimated in clinical practice [45]. Finally, how such agents predispose individuals with HLA DQB1*06:02 to narcolepsy still remains unclear and should be investigated further [6,11,12].

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Conflict of interest

The author declares no conflict of interest.

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