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The Etiology of Narcolepsy

Abstract

Narcolepsy is a neurological disorder that affects the nervous system leading to the loss of the brain's ability to regulate sleep-wake cycles. It is characterized by diurnal somnolence and episodes of short duration sleep. Symptoms include repeated daytime sleepiness, similar to how people who do not have narcolepsy feel after 24–48 hours of sleep deprivation, as well as disturbed sleep, which often is confused with insomnia. Another common symptom of narcolepsy is cataplexy, a sudden and transient episode of muscle weakness accompanied by full conscious awareness, frequently triggered by emotions such as laughing, crying, terror, etc. affecting almost 70% of people who have narcolepsy. Recent laboratories research on hypocretins (oroxins) has led to a greater understanding of this debilitating condition. The goal of this minireview is to describe briefly the etiology of narcolepsy.

Keywords: Narcolepsy; Etiology; Hypocretins; Cataplexy; Deprivation; Sleepiness; Somnolence; Symptoms; Neurologist; Hypothalamus; Hypothesis; Orexin; Dynorphin; Narcoleptics; Hormone

Short Communication

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Toward the end of World War I, an epidemic of encephalitis swept across Europe. In many patients, this caused crushing sleepiness, and the Austrian neurologist Constantin von Economo [1] found that these patients usually had inflammation and injury to the posterior hypothalamus. He went on to speculate that the sleepiness of narcolepsy might be caused by injury to this region, but for decades this hypothesis could not be tested as so little was understood about the cells and functions of the hypothalamus. In 1998, two labs independently discovered a pair of hypothalamic neuropeptides termed orexin-A and -B (or hypocretin 1 and 2) and their receptors (OX1 and OX2) [2,3]. The orexins have since been demonstrated to play essential roles in maintaining wakefulness and regulating transitions between sleep and wake [4-8]. The following year, another pair of research teams found compelling evidence that narcolepsy could be caused by a loss of orexin signaling. Masashi Yanagisawa's group produced an orexin ligand knockout mouse with sleepiness and cataplexy strikingly similar to human narcolepsy [4]. Simultaneously, Emmanuel Mignot's group demonstrated that canine narcolepsy resulted from a mutated orexin receptor [9]. The definitive link between narcolepsy and orexin followed when researchers demonstrated a lack of orexin peptides in the hypothalamic and CSF of narcolepsy patients [10-12]. Further research has demonstrated that nearly 90% of the orexin-producing neurons are lost in human narcolepsy with cataplexy. The endogenous opiate dynorphin and NARP (a protein involved in glutamate signaling) are also produced by the orexin neurons, and both of these markers are absent in the lateral hypothalamus of patients with narcolepsy [13,14]. This cell loss seems highly selective, as neurons producing melanin-concentrating hormone, which are intermingled with the orexin neurons, seem completely unaffected [10,11]. Collectively, these studies provide strong evidence that some process selectively destroys the orexin neurons. These studies focused on patients that have narcolepsy with cataplexy, yet much less is understood about the neuropathology of narcolepsy without cataplexy. This type of narcolepsy affects approximately half of all patients with narcolepsy, and the severity of symptoms is often less than in patients with cataplexy [15]. Though little is known about the underlying neuropathology, narcolepsy without cataplexy may simply be caused by less severe injury to the orexin neurons [16], resulting in mainly sleepiness and a small reduction in CSF orexin level [12,17]. Mild to moderate loss of the orexin neurons has also been demonstrated in Parkinson's disease [18] and traumatic brain injury [19], disorders that often produce sleepiness but no cataplexy. In addition to controlling sleep/wake states, the orexin neurons also regulate metabolism, feeding, reward, and autonomic tone, resulting in additional symptoms [20-22].

Many studies have indicated an association between narcolepsy and obesity, where it has been demonstrated that narcoleptics were more likely to be overweight compared to non-narcoleptics s [23-25]. For example, weight gain is common at the onset of narcolepsy, especially in children, perhaps from a reduction in basal metabolic rate [26,27].

The National Institute of Neurological Disorders and Stroke (NINDS) sponsored researchers are conducting studies devoted to further clarifying the wide range of genetic factors-both HLA genes and non-HLA genes-that may cause narcolepsy [28]. A greater understanding of the complex genetic and biochemical bases of narcolepsy will eventually lead to the formulation of new therapies to control symptoms and may lead to a cure. Researchers are also investigating the modes of action of wake-promoting compounds to widen the range of available therapeutic options [29]. Abnormal immunological processes may be an important element in the cause of narcolepsy. NINDS-sponsored scientists have demonstrated the presence of unusual, possibly pathological, forms of immunological activity in narcolepsy. Further, Strep throat is now suggested to be involved as a trigger in some predisposed individuals [30]. These researchers are now investigating whether drugs that suppress immunological processes may interrupt the development of narcolepsy [30]. A more comprehensive understanding of the complex biology of

sleep will undoubtedly further clarify the pathological processes that underlie narcolepsy and other sleep disorders. Future neurobiology research shall reveal more facts about the etiology of narcolepsy.

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